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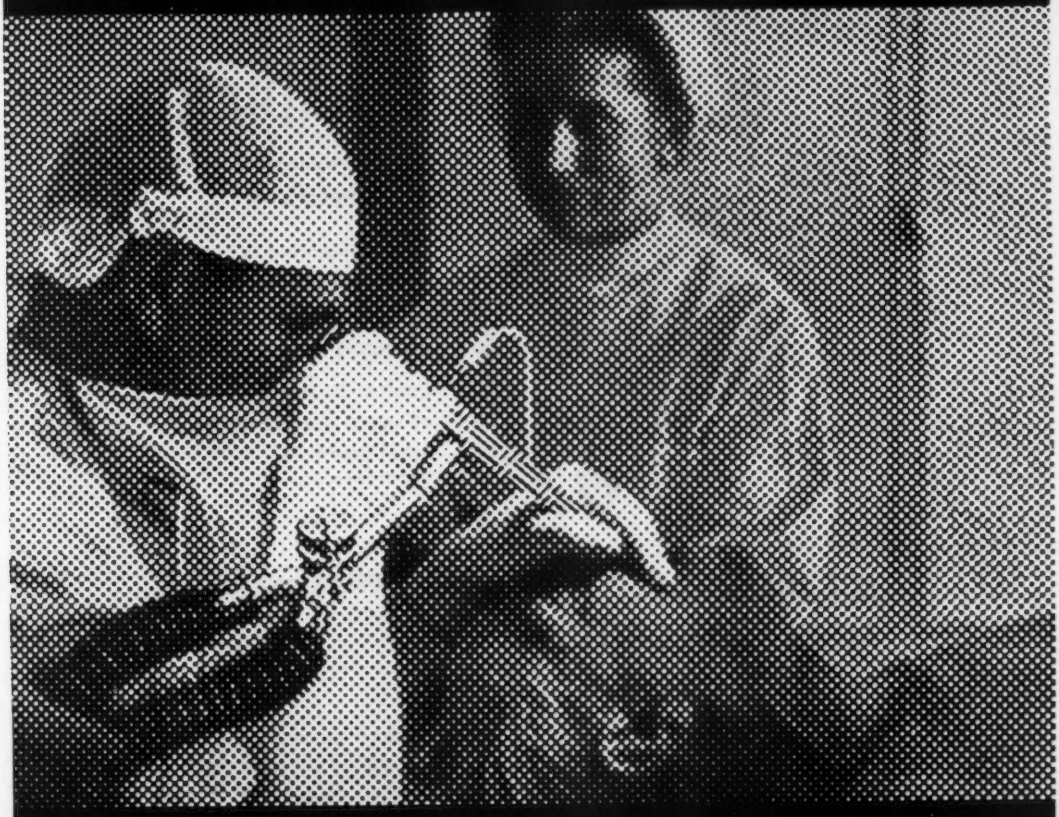

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*B. Sheiner, *C.A.M.J.*, *83*, 1377-78, 1960.

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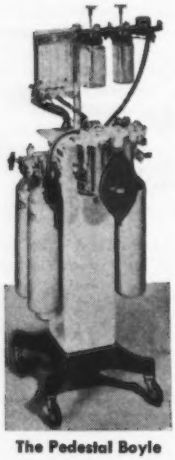

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ANAESTHESIA FOR SURGICAL CORRECTION OF VASCULAR RING*

THOMAS J. MCCAUGHEY, M.B., B.CH., D.A.†

ANOMALIES of the arch of the aorta and the vessels arising from it are not uncommon. In themselves they do not endanger life, nor are they usually associated with congenital heart disease. When they cause obstruction of the oesophagus or trachea, however, surgical intervention is often needed to prevent an early respiratory death.

HISTORY

One of the earliest references in the literature seems to be that of Hommel in 1737, whose case prompted Quain[1] to describe these anomalies in detail in 1844. The obstruction of the oesophagus associated with an aberrant right subclavian artery was graphically described by Bayford[2] in 1794, whose patient "worn out with fatigue and famine . . . sank into the grave" at the age of 62 years. Gross[3] reported the first successful operation to break a vascular ring in 1945. Ten years later[4] he reviewed experiences in 70 cases with five deaths, all in the type known as double aortic arch. Potts[5] in 1956 described his experiences with 28 cases, six of whom died. According to Apley,[6] five clinical reports of these anomalies had appeared in the British literature by 1957. Neuhauser[7] has been prominent in focussing attention on the radiological diagnosis. Many centres doing paediatric surgery have now had experience with these cases.

CLASSIFICATION

An excellent account of the embryology and a comprehensive classification is given by Harley.[8] Many of the possible variants he lists have yet to be described. In addition, Harley gives a useful clinical classification into three groups:

(1) Those vessels which compress only or mainly the oesophagus. This comprises mainly the subclavian artery arising from the distal part of the aortic arch and going behind the oesophagus to the opposite axilla. Also included here is a ductus arteriosus communicating with a right-sided aorta and passing behind the oesophagus to the left pulmonary artery (Fig. 1).

(2) Vessels compressing only the trachea such as anomalous innominate or left common carotid arteries (Fig. 3).

(3) Those vessels which compress both structures. This includes all other variants of vascular ring, such as double aortic arch (Fig. 2).

*Presented at the Annual Meeting, Canadian Anaesthetists' Society, May 15–18, 1961.

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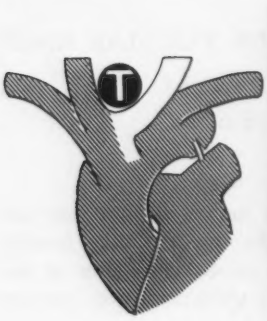

FIGURE 1

FIGURE 2

FIGURE 3

CLINICAL PICTURE AND DIAGNOSIS

Not all vascular ring anomalies give rise to serious symptoms. When these occur the initial picture depends on whether the oesophagus or trachea is more compressed. Oesophageal obstruction in infancy leads to regurgitation and choking during and after feeding, and inevitably causes aspiration pneumonia. When tracheal compression is present the infant has continuous difficulty in breathing with obstructive sounds which can be heard both in inspiration and expiration. In severe cases the baby assumes a hyper-extended position to make breathing easier. Attacks of cyanosis and unconsciousness occur. Respiratory infections and broncho-pneumonia are common and prolonged. With these complications the signs of respiratory obstruction are very severe. Tracheostomy may seem indicated but is usually useless, for this tracheal obstruction is often just above the carina. One of our patients (Case 2) had a tracheostomy to tide him over a severe bout of pneumonia, but his obstruction was subsequently found to be mainly oesophageal.

Radiological examination of the oesophagus and trachea using contrast media in very small amounts usually makes the diagnosis with amazing accuracy. According to Gross[4] radiological evidence of oesophageal and tracheal compression in infancy in the absence of a mediastinal tumor is almost diagnostic of some form of vascular ring. The oesophagus is usually seen to be displaced forward and indented posteriorly at about the level of thoracic 2 or 3. The degree and site of tracheal compression are usually reported accurately by the radiologist. This compression will be seen to vary, sometimes considerably, with the phases of respiration. Time is well spent by the anaesthetist in study of these films. We have not found tracheoscopy and oesophagoscopy necessary, nor is angio-cardiography usually indicated. These infants are often very ill.

CASE HISTORIES AND RESULTS

Some of the main points concerning the twelve patients in this series are shown in Table I. Surgical correction of the vascular anomalies was performed in eight of these patients without mortality and with satisfactory clinical and radiological

TABLE I

CASES WITH VASCULAR RING ANOMALIES

Case	Age	Predominant symptoms	Type of lesion	Operation	Anaesthetic difficulties	Postoperative complications	Result
1	20 mos.	Difficulty in swallowing, respiratory infections	Right descending aorta, aberrant left subclavian, and ligumentum arteriosus	Division left subclavian and ligumentum arteriosus	No airway problems	None	Good; alive and well
2	6 wks.	Severe pneumonia	Aberrant right subclavian artery	Division right subclavian and forward fixation of great vessels	No airway problems	None	Good; alive and well
3	6 mos.	Severe pneumonia	Fallot's Tetralogy and aberrant subclavian artery	None			Still not operated; condition no worse
4	27 mos.	Persistent cough, extensive right-sided pneumonia	Right descending aorta, left ligamentum arteriosum	Division ligamentum arteriosum, forward fixation of great vessels	Momentary obstruction during dissection, around trachea	None	Satisfactory; alive and well
5	6 wks.	Attacks of respiratory obstruction and cyanosis	Double aortic arch with ductus arteriosus	Division anterior arch and ductus arteriosus	Deliberate right lung anaesthesia only; recurrent laryngeal and probably left phrenic nerve also inadvertently cut	Obstruction; bronchoscopy, tracheostomy	Now two years of age; alive and well
6	3 mos.	Blue spells while feeding, severe broncho-pneumonia and status epilepticus	Aberrant right subclavian artery	None			Not operated; died from intercurrent medical disease

TABLE I (Concluded)

Case	Age	Predominant symptoms	Type of lesion	Operation	Anaesthetic difficulties	Postoperative complications	Results
7	2 mos.	Some choking and cyanotic attacks	Probably right aortic arch with aberrant left subclavian artery	none			Has done well without operation
8	4 mos.	Wheezing	Double aortic arch	Division of smaller posterior arch	Intubated beyond obstruction; no difficulties	Left-side pneumonia 4 days postoperatively	Good; alive and well
9	2 wks.	Wheezing, crowing when feeding, and cyanosis	Double aortic arch, right descending descending aorta, ductus arteriosis	Division anterior arch and ductus arteriosus	Endotracheal tube placed distal to obstruction; no difficulties	None	Good, clinically and radiologically
10	7 mos.	Repeated attacks pulmonary infection	Right descending aorta, aberrant left subclavian and ductus arteriosus	Division left subclavian and ductus arteriosus, forward fixation of great vessels	During dissection intermittent obstruction of left main bronchus occurred	None	Has done well
11	1 day	Oesophageal atresia and tracheo-oesophageal fistula	Aberrant right subclavian artery seen during surgery	Repair oesophageal atresia and tracheo-oesophageal fistula; no vascular surgery	None	None	Doing well; no clinical or radiological evidence to justify further surgery
12	1 mo.	Pneumonia	Right-sided arch right descending aorta, aberrant left subclavian, and ductus arteriosus	Division left subclavian and ductus arteriosus, forward fixation of pulmonary artery	None with controlled respiration	No immediate complications; admitted again with aspiration pneumonia	Now alive and well

results. In one of the remaining four patients (Case 11) an aberrant right subclavian artery was seen during surgery done to repair an oesophageal atresia and tracheo-oesophageal fistula. This vessel was not resected and there has been no subsequent indication to do so. In Case 3 an aberrant subclavian artery was diagnosed radiologically in conjunction with a Fallot's tetralogy. This patient awaits surgery for his heart condition. One patient (Case 7) has not had severe enough symptoms to warrant surgery, while the remaining patient (Case 6) died in status epilepticus with overwhelming broncho-pneumonia before surgery could be performed. A more detailed description of the salient points in these case histories follows.

Case 1

A girl was admitted at 20 months of age with a history of frequent respiratory infections and difficulty in swallowing. Radiological examination of the chest revealed that the oesophagus was displaced sharply to the left at the level of thoracic 2 and 3 and that a posterior filling defect was present (Fig. 4). A tracheogram was done under general anaesthesia with nitrous oxide, oxygen, and trichlorethylene. This revealed a minor defect on the right side without any marked narrowing of the trachea. At operation the surgeon found a right-sided descending aorta with the left subclavian artery and the ligamentum arteriosum both arising from it and passing behind the oesophagus (Fig. 5). Both these structures were divided and the postoperative condition was much improved. For anaesthesia nitrous oxide, oxygen, d-tubocurarine, and minimal ether were given. There were no airway problems involved here.

Case 2

This patient was admitted at six weeks of age with very severe pneumonia and respiratory obstruction. The diagnosis of vascular ring was entertained at that time, but because of the respiratory obstruction it was decided to perform tracheostomy. When the patient had sufficiently recovered and the tracheostomy had been removed, a barium swallow revealed that the oesophagus was displaced forward and indented posteriorly at the level of thoracic 2 and 3 (Fig. 6). A tracheogram revealed only a minor defect on the right side of the trachea about 2 cm. proximal to the carina. Anaesthesia for thoracotomy was nitrous oxide, oxygen, and ether by oral endotracheal tube and no airway difficulties were encountered. A right subclavian artery arising from the descending aorta was found coursing behind the oesophagus (Fig. 7). This was divided and the great vessels were freed forward from the front of the trachea and fixed anteriorly to the back of the sternum to prevent compression of the trachea. The child has done well since.

Case 3

This child was admitted at six months of age with severe pneumonia and cyanotic heart disease. Radiological examination of the chest revealed a picture suggestive of Fallot's tetralogy, and barium swallow showed an oblique defect in the oesophagus probably due to an aberrant subclavian artery. He improved on being treated with high humidity and has since done well, not requiring further hospital admissions. He is now three years of age.

Case 4

This 27-month-old child was first admitted with extensive right-sided pneumonia. This cleared up with antibiotic therapy except for a persistent cough. About four and one-half months later she was re-admitted when a barium swallow revealed that the oesophagus was compressed both posteriorly and bilaterally just above the level of the carina. Slight narrowing of the trachea was evident at the same level. For thoracotomy, anaesthesia was induced with cyclopropane following rectal pentothal; succinylcholine was used for

FIGURE 4

intubation; and respirations were controlled with the Jefferson Ventilator, Gallamine being given for longer acting muscle relaxation. After a fairly lengthy surgical dissection a ligamentum arteriosum, communicating with the left pulmonary artery and a right-sided descending aorta, was found and divided. As recommended by Gross, the great vessels were also fixed forward to the sternal region by sutures. Since there was no great compression of the trachea, the airway was quite clear during the early part of anaesthesia. A monaural stethoscope placed at the back of the chest enabled the anaesthetist to monitor the breath sounds continuously. However, during the dissection

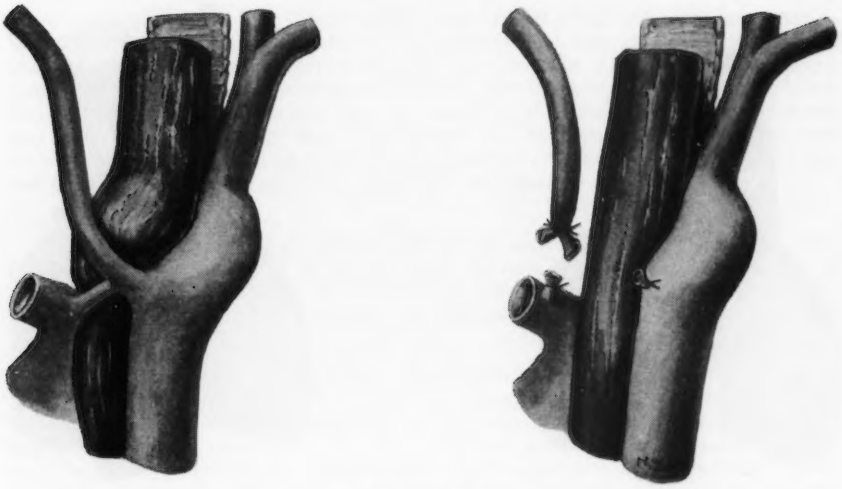

FIGURE 5

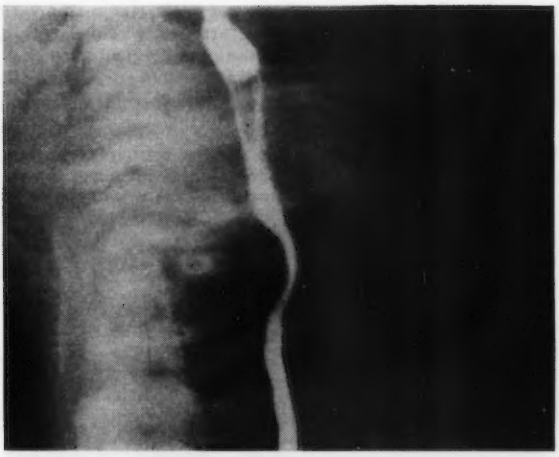

FIGURE 6

anterior to the trachea the respiratory exchange became inadequate. The surgeon stopped work on request, the endotracheal tube was adjusted, and anaesthesia was manually controlled from this point onward. Postoperatively the child did well, apart from a slight cough, and has been free of symptoms since.

Case 5

This little boy was admitted at six weeks of age with a history of respiratory difficulty from birth with severe attacks of respiratory obstruction and cyanosis. Radiological examination of the chest revealed a persistent indentation of the oesophagus posteriorly

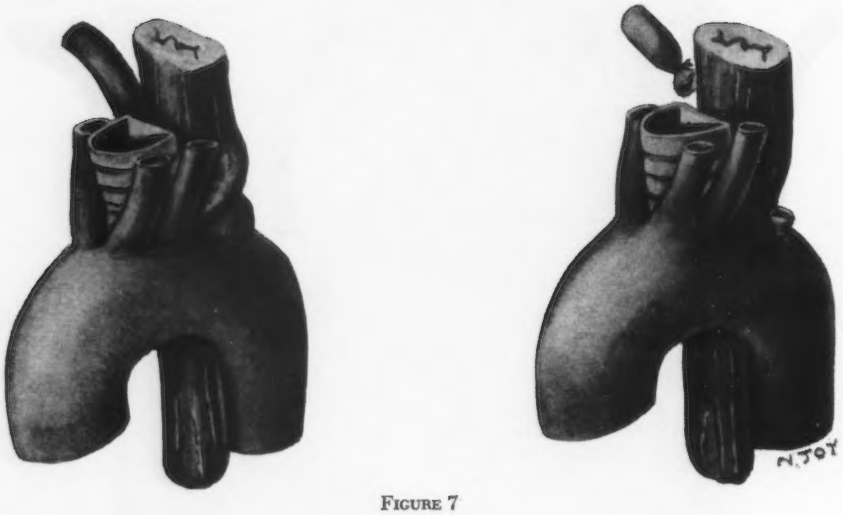

FIGURE 7

and on the right and left just above the level of the carina together with considerable narrowing of the trachea at the same level (Fig. 8). At thoracotomy the patient was found to have a double aortic arch and ductus arteriosus. The larger arch (developmentally the right arch) passed posteriorly to the oesophagus as usual, but the smaller arch (anterior) gave off the left common carotid and left subclavian arteries. Accordingly, this arch was divided between the left common carotid and subclavian arteries. It is important to leave the left common carotid artery coming off the proximal part of aortic arch rather than have the blood enter it in a retrograde fashion. The ductus arteriosus was divided and the vessels freed forward off the front of the trachea and fixed to the back of the sternum. Unfortunately, during the dissection, the recurrent laryngeal

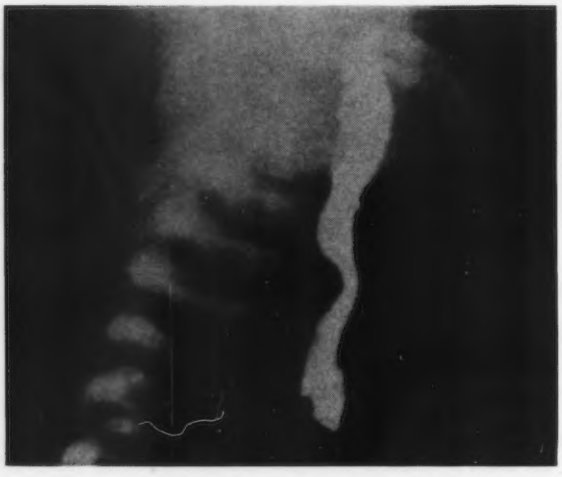

FIGURE 8

nerve and probably the left phrenic nerves were cut—this led to trouble later. Anaesthesia was induced with cyclopropane. An endotracheal tube was inserted past the obstruction and throughout most of the procedure only the right lung was ventilated. Controlled respiration using small doses of succinylcholine intermittently was employed. The patient did well for some time after extubation but then suddenly became obstructed and emergency bronchoscopy and tracheostomy were needed. Bronchoscopy was done on two other occasions during a stormy convalescence. He was finally discharged two and one-half months after operation. He is now two years of age and doing well.

Case 6

This infant was admitted at three months of age with a history of blue spells when feeding. She only weighed 7 lb. at this time. She was discharged and readmitted at seven months of age in status epilepticus and with severe broncho-pneumonia from which she subsequently died. At autopsy, an aberrant right subclavian artery was found.

Case 7

This little boy has had a long history of admissions to hospital from two months of age with attacks of choking and cyanosis on crying. Radiological examination of the oesophagus showed posterior indentation of the oesophagus at the level of thoracic 2 and 3 and bilateral constriction. The trachea did not seem to be much narrowed. The most recent tracheograms and oesophagrams have suggested a right-sided aortic arch. There is not enough evidence of obstruction of the trachea or oesophagus to justify surgical intervention.

Case 8

At four months of age this boy was admitted with a history of wheezing. Before admission a diagnosis of an enlarged thymus was made at another hospital and treated by radiation. As this did not improve the complaint, the patient was admitted to our hospital. Radiological examination of the chest revealed that the oesophagus and trachea were both compressed and narrowed, the indentation in the trachea being approximately 2 cm. proximal to the carina (Figs. 9 and 10). As in many of these cases the narrowing of the trachea was seen to vary considerably with different phases of respiration. The diagnosis was vascular ring and thoracotomy was accordingly performed. For this the

FIGURE 9

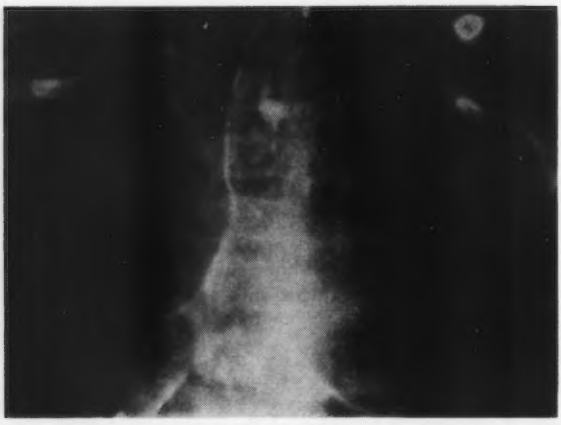

FIGURE 10

patient was induced with cyclopropane following a small dose of rectal pentothal, intubated following succinylcholine relaxation, and maintained on nitrous oxide, oxygen, and ether. A No. 1 Magill endotracheal tube was used and there was no great trouble with the airway, to our surprise. A double aortic arch was found with the smaller one going posteriorly. This was divided and the constriction relieved (Fig. 11). The infant had evidence of left-sided broncho-pneumonia developing about four days postoperatively. This cleared up and the child was discharged in good condition.

Case 9

This boy was admitted at two weeks of age with a history of wheezing respiration, crowing when feeding, and attacks of cyanosis. Visualization of the oesophagus and trachea by contrast medium revealed that the oesophagus was both deviated and compressed at about the level of the aortic arch and that the trachea was indented on the right and posteriorly about 1.3 cm. above the carina (Fig. 12). An effort was made to place the tip of the endotracheal tube distal to the obstruction of the trachea. This was apparently successful and anaesthesia was relatively uneventful. At thoracotomy a double aortic arch with a right-sided descending aorta was dissected out. The anterior limb was divided, as well as a ductus arteriosis, and the trachea and oesophagus freed out (Fig. 13). Postoperatively the chest gradually cleared and re-examination showed that the obstruction to the oesophagus and trachea has been largely removed.

Case 10

This seven-month-old boy had repeated attacks of pulmonary infection, especially in the right upper lobe. Bronchoscopy on three occasions was negative. Examination of the oesophagus using contrast medium revealed marked posterior indentation and displacement to the left of this structure at the level of thoracic 3. Narrowing of the trachea just above the carina was also seen. At operation a right-sided descending aorta with the left subclavian coming off and coursing behind the oesophagus and a patent ductus arteriosus completed the ring. After careful dissection the left subclavian and ductus arteriosus were divided. The pulmonary artery and left common carotid were sutured forward to the sternum to release pressure on the trachea. Anaesthesia was induced with cyclopropane and intermittent succinylcholine given to enable respirations to be controlled throughout the procedure. During the dissection it was very difficult at times to inflate the left lung and this was to be expected. A reinforcing dose of 0.2 mg. of

FIGURE 11

FIGURE 12

atropine was given intravenously about three hours after the start of surgery and during the dissection around the oesophagus when some heart slowing was noted. The post-operative course was fairly uneventful and the last X-rays showed the oesophagus not to be obstructed.

Case 11

This infant girl was admitted to our hospital a few hours after birth with a diagnosis of oesophageal atresia and tracheo-oesophageal fistula. This was satisfactorily repaired. During the procedure an aberrant right subclavian artery was noted by the surgeon who judged that it was not compressing the trachea and left it alone. Subsequently this vessel was seen pulsating on oesophagoscopy performed at eight months of age, although it was not causing obstruction. Radiological examination of the chest using a cine machine demonstrated that there is some slight indentation of the oesophagus by the aberrant subclavian artery and some occasional narrowing of the trachea. However, so far there have been no symptoms to justify further surgical intervention.

Case 12

An infant boy was admitted at one month of age because of an upper respiratory infection and right upper lobe pneumonia. Radiological examination of the oesophagus and trachea revealed posterior indentation of the oesophagus and an oblique defect probably due to an aberrant vessel. There was as well a well-defined narrowing of the trachea just above the carina. After induction with cyclopropane and intubation following succinylcholine, a No. 1 Davol endotracheal tube was easily introduced past the obstruction to the right main bronchus. This was confirmed by continuous auscultation of the chest. The tube was then gradually withdrawn till aeration of both lungs was present. Respiration was controlled throughout, and hypothemia to 31° C. induced. Rewarming to 33.0° C. was done before the end of surgery. A right-sided aortic arch and right descending aorta were found with the left subclavian artery and the ductus arteriosus both coming off on the right side and winding round posteriorly to the oesophagus. These vessels were divided and the pulmonary artery fixed anteriorly to the sternum to relieve compression on the trachea. During the dissection, spontaneous

FIGURE 13

respiration inadvertently occurred on one occasion and aeration at once became inadequate. With controlled respiration, on the other hand, ventilation was always efficient. The postoperative course of this infant from a respiratory point of view was fairly satisfactory. The baby was discharged 16 days postoperatively but has had to be readmitted on two occasions because of pneumonia following aspiration. However, he now seems to be doing quite well.

Suggested Management of Anaesthetic Problems

The preoperative condition of these patients is often serious. They must frequently be accepted for anaesthesia with severe respiratory infection still present. It may be almost impossible to keep a clear airway throughout the surgical procedure. The immediate postoperative period on occasion may be worse than before surgery.

The anaesthetist must carefully assess the patient both from the clinical and radiological findings. The greatest difficulty and stormiest postoperative course may usually be expected in patients with double aortic arch. The site of tracheal obstruction, when present, is important to the anaesthetist. If situated just above the carina, placing the tip of the endotracheal tube distal to the obstruction may mean using one lung anaesthesia only, as in Case 5. A selection of endotracheal tubes of different sizes and lengths must be carefully assembled.

We have favoured the use of fairly heavy premedication with atropine only, usually 0.24 mg. to 0.3 mg. in infants under six months of age. In one of our patients (Case 10) a reinforcing dose of atropine was given because of heart slowing during the dissection around the oesophagus. Hypoxia might have contributed to this bradycardia.

In the larger patients we have occasionally given rectal pentothal to make induction of anaesthesia easier. Usually, however, anaesthesia was induced with cyclopropane and oxygen. Smith[9] has questioned the advisability of trying to insert the endotracheal tube past the tracheal obstruction, while Wetchler and McQuiston[10] have tended to favour this technique. Wherever the tube is placed, controlled respiration is absolutely essential. The oxygen demands of the muscles of respiration may make a marginal hypoxic state serious. In addition, whereas adequate ventilation can be maintained with controlled respiration, the onset of spontaneous breathing often leads to immediate obstruction from mediastinal movement. Finally, only with controlled respiration can the surgeon have a quiet field for what is usually a lengthy and dangerous dissection. Intermittent succinylcholine together with minimal fluothane using a T-piece technique works well. We have tried to place the tip of the endotracheal tube distal to the tracheal narrowing when this is marked. Moderate hypothermia to 32.0° C. helps to tide the patient over periods of hypoxia which can occur during the dissection. The breath sounds must be continuously monitored by stethoscope, which can be placed in the axilla opposite to the surgical incision or at the back of the chest. The anaesthetist must watch the field, as sudden obstruction is usually related to surgical interference. The surgeon and his assistants must immediately desist when this occurs. Rapid blood loss can occur and must be immediately replaced. The infant's blood-pressure cuff and monaural stethoscope are very important pieces of paediatric equipment here.

We have not resorted to cutting side-holes in the endotracheal tube, although a single suitably-placed hole for the upper lobe bronchus may help when the right main bronchus is deliberately intubated. Neither have we encountered any case where the lumen of the trachea was so small that a conventional endotracheal tube of suitable size would not pass. This difficulty has been described by Wetchler and McQuiston. With the range of small plastic endotracheal tubes now commercially available even the smallest trachea can be intubated. Frequent suctioning through the endotracheal tube must be done regularly, whether the breath sounds are moist or not. Almost all the dissection is around the carina and the trauma involved frequently causes bleeding into the lumen of the trachea.

In the postoperative period the patient is placed in an atmosphere of maximal humidity. Antibiotics and steroids may be necessary. Tracheostomy is to be avoided although sometimes, as in Case 5, it may be unavoidable; in this case cutting the recurrent laryngeal nerve complicated matters. An endotracheal tube small enough to pass through the tracheostomy tube and beyond the tracheal obstruction must be to hand. Moderate hypothermia, under medical supervision, in the postoperative period may be needed to tide the infant over recurring bouts of obstruction and hypoxia. These patients ought to have follow-up radiological examinations some months after operation to assess the effectiveness of surgery.

Summary

The literature on vascular ring anomalies is briefly reviewed. The results of some recent cases at The Children's Hospital, Winnipeg, are presented.

The anaesthetist must study the clinical and radiological findings carefully. Controlled respiration through an endotracheal tube of suitable size and length is used together with moderate hypothermia. The airway is precarious and complete co-operation between anaesthetist and surgeon is essential. Blood loss may be sudden and severe.

In the postoperative period, tracheostomy is to be avoided if possible. Maximum humidity, antibiotics, and steroids are needed.

Acknowledgments

My thanks are due to Professor C. C. Ferguson, Drs. L. L. Whytehead and M. B. Perrin, whose patients are reported here, Miss Nancy Joy, Medical Artist, Department of Surgery, University of Manitoba, who drew the figures, and to Mr. Tony Gibson, Medical Photographer, The Children's Hospital, who did the photographs.

Résumé

Une grande partie de l'anatomie des anomalies populairement connues sous le nom d'anneau vasculaire, a été démontrée depuis plus de deux siècles, mais c'est Grosse de Boston qui a opérè le premier cas avec succés en 1945. Depuis cette époque de nombreux centres contribuèrent des rapports qui ont permis de connaître davantage les problèmes à la fois en chirurgie et en anaesthésie.

Cet article est un rapport d'expériences avec des cas semblables, opérès à l'Hôpital des Enfants, de Winnipeg, dans les années récentes.

Les anomalies vasculaires peuvent être divisées cliniquement en trois catégories. Dans la première catégorie, le vaisseau anomal ou les vaisseaux anomaux ressèrent surtout l'oesophage; dans la seconde, c'est la trachée-artère qui est obstruée; mais dans la troisième classe un anneau vasculaire complet est la cause de l'obstruction à la fois de l'oesophage et de la trachée-artère.

C'est souvent dans un état sérieux que ces malades sont acceptés pour l'anaesthésie, aussi ils souffrent parfois d'infections respiratoires sévères. Il est obligatoire de controler le souffle pendant toute la procédure, et le risque d'anoxèmie qui très souvent arrive causé par l'obstruction, est diminué par l'usage d'une hypothermie modérée à 32° ou 31° C.

Dans un cas sévère nous avons essayé de placer notre tube après l'obstruction dans la trachée-artère. En employment un stéthoscope bien placé, les sons de la respiration doivent être continuellement auscultés. Le traumatisme chirurgical bien souvent est la cause de saignement dans la trachée, si bien qu'il est nécessaire d'aspirer le tube à intervals réguliers et fréquents. L'anaesthésiste doit regarder la procédure chirurgicale tout le temps, ca un saignement soudain pourrait arriver. Si le chirurgien est la cause de l'obstruction trachéale, on lui demande d'arrêter immediatement.

Après l'opération il vaut mieux éviter la trachéotomie. Un maximum d'humidité, des antibiotiques et de cortisone sont administrés. Une hypothermie modérée aurait peut-être besoin d'être continuée pendant quelques jours.

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STUDIES WITH INTRA-ARTERIAL SUCCINYLCHOLINE AND ITS HYDROLYSIS PRODUCTS*

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IN THE COURSE of the past eight years, during which succinyl(di)choline has become established as a muscle relaxant drug of great utility in clinical anaesthetic practice, there have been numerous attempts to identify the causes of the occasional cases of prolonged relaxation resulting from its use.[1-8] A number of clinical entities have been described which are at times associated with a dramatic prolongation of the muscle relaxant activity of succinyldicholine: these have inc'uded electrolyte derangements, acid-base imbalance, cachexia, impaired renal function, and abnormal cholinesterase activity.[9] The present study is concerned not with these abnormalities, but with mechanisms by which succinyldicholine's action may be prolonged in the patient whose neuromuscular physiology is normal prior to the administration of this drug.

The cumulative effect of muscle relaxant drugs such as gallamine triethiodide and d-tubocurarine chloride is well recognized, and consequently the anaesthetist is on firm ground in his effort to limit total dosage of these drugs. In the use of succinyldicholine, however, cumulative effect was not widely recognized in the early years of its use; and at present the mechanisms by which its action persists longer than would have been expected, the fact that the nature of the block it produces changes with increasing dosage and duration of use, and the fact that the need for increasingly rapid administration reveals a type of tachyphylaxis[10] are subjects for intense speculation and investigation.

The concept that the action of succinyldicholine upon neuromuscular transmission is as evanescent as the drug's hydrolysis is rapid, and that therefore no ceiling need be imposed upon clinical dosage, is no longer tenable. For, in fact, it has been demonstrated that the first-stage hydrolysis product of succinyldicholine, which is succinylmonocholine (Fig. 1), is itself a muscle relaxant drug of weaker but more prolonged action than its precursor.[11] This information by itself would perhaps be sufficient reason for the limitation of total dosage of succinyldicholine, despite the fact that the monocholine ester is hydrolised in a reasonably short space of time.[12, 13] However, further reason for the limitation of total dosage is suggested by the discovery that choline, an hydrolysis product of both succinyldicholine and succinylmonocholine, also has significant actions upon neuromuscular transmission.[14-16]

An extensive study of the effect of choline on neuromuscular transmission in the human has been carried out by Grob and his co-workers.[14, 16] Acetylcholine was

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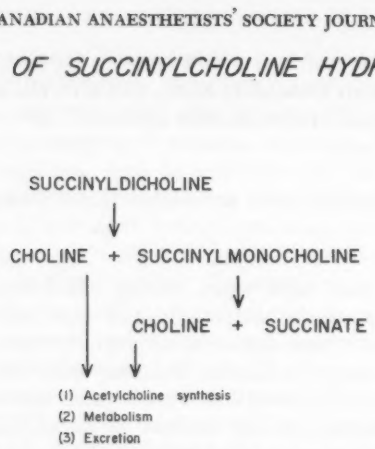

FIGURE 1. Hydrolysis of succinyldicholine to choline and succinylmonocholine, and the latter's further hydrolysis to choline and succinate.

administered intra-arterially and muscle action potentials were recorded after nerve stimulation: these experiments demonstrated that, following the administration of 1 mg. of acetylcholine and the immediate reaction to it, there existed a secondary depression of action potentials which lasted from 30 minutes to one hour, apparently due to the choline moiety released in the course of the hydrolysis of acetylcholine: as the dosage of choline was increased, the characteristics of the neuromuscular block changed from those of a depolarizing type to those of a competitive block. It is worth noting that the amounts of choline released by the hydrolysis of acetylcholine in these experiments were very small in comparison to the amounts that would be released by the hydrolysis of a clinical dose of succinyldicholine, which is 80 per cent choline by weight.

Hutter[15] also has studied the effect of choline on neuromuscular transmission, and, using the anaesthetized cat as a subject, has demonstrated similar response to the administration of choline intra-arterially. He observed three different types of response to choline, depending upon the size of the dose: in low dosage, choline appeared to potentiate neuromuscular transmission, an effect ascribed to the repetitive response of individual fibers to a single nerve stimulus; with a larger dose, this potentiation was followed by depression of neuromuscular transmission; and with the largest doses, fasciculations occurred in the muscles supplied by the artery employed for the injection, and then depression ensued.

Studies on the fate of choline when administred orally and intravenously in man[17, 18] reveal that it is excreted unchanged in the urine in only small amounts, and that there is an absence of any symptoms referable to an effect on neuromuscular transmission when over 2 gm. of choline chloride are administered intravenously. In view of the effect produced by as little as 0.8 mg. of choline given intra-arterially in Grob's studies,[16] it would appear that there is a mechanism for very rapid binding or clearing of excess choline in the circulatory tree.

Normal choline plasma levels were found by Bligh to be 1.1 to 2.1 μg per ml., remaining very constant in the same individual over prolonged periods of time.[19]

The present study was undertaken to investigate further the effects of choline upon neuromuscular transmission, in an attempt to point to a correlation between prolongation of the action of succinyldicholine and the accumulation of its hydrolysis products, particularly choline.

Methods and Material

Cats were anaesthetized with intravenous pentobarbital, in a dosage of 20 mg./kg., with small subsequent doses when needed, and the nerve supply to the anterior tibial group of muscles was exposed and stimulated electrically at varying rates, the individual stimuli being supramaximal. Muscle action potentials were recorded from electrodes on the tibialis anticus, being read visually from an oscilloscope screen which was calibrated frequently with stimuli of known strength; gross estimates of muscle activity were also made, the best, and surprisingly consistent, means of determination being the extent to which the movement of a twitch was transmitted to the fur of the paw, lower leg, and thigh. The femoral artery in the upper thigh was employed as the route for intra-arterial injections of the salts of succinyldicholine and choline, and of the iodide salt of succinylcholine: chloride dosages mentioned refer to the amount of the salt.

Intravenous and Intra-arterial Succinyldicholine

Intermittent intravenous doses of succinyldicholine were administered in amounts of .06 mg./kg., and the doses were spaced about 10 to 14 minutes apart (Fig. 2). The response to each injection was quite uniform, and within seven to ten minutes after each injection the muscle action potential returned to about 75 per cent of its control value and the strength of the muscle twitch in response to stimulation returned to an approximately normal value.

The response of the muscle to repeated intra-arterial administrations of succinyldicholine in a dosage of 0.05 mg./kg., using a fresh animal, was strikingly different (Fig. 3). After the second injection of 0.12 mg., the gross estimate of muscle strength in response to stimulation climbed fairly rapidly toward normal; however, the length of time after the third injection until the first faint twitch increased from the previous five minutes to eight minutes, and the time taken for recovery to a normal response from this faint twitch increased from the previous three or four minutes to eleven minutes. Paralysis was complete after all these intra-arterial doses, whereas there was always a detectable twitch and accompanying muscle action potential after intravenous doses.

A large (1 mg.) dose in the same animal, given by the same intra-arterial route, produced severe weakness of the muscle for over one hour, and evidence of muscle fatigue at the end of this period of time.

Intra-arterial Succinylmonocholine and Choline

Succinylmonocholine produced two noticeable effects. First of all, when it was given in a dosage calculated to be such as would be released by hydrolysis

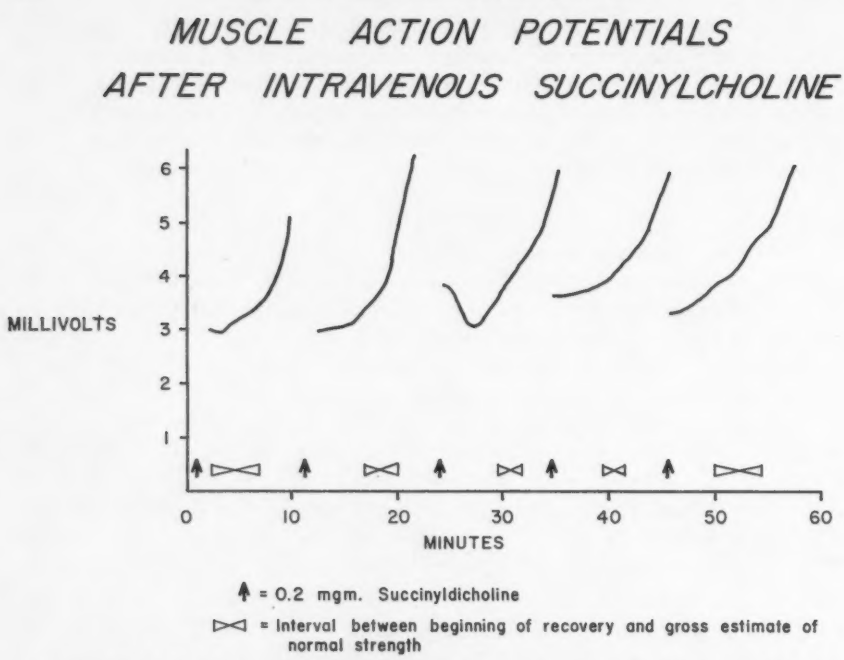

FIGURE 2. Effect of intermittent intravenous doses of succinyldicholine (0.06 mg./kg.) on the muscle action potential of tibialis anticus of the cat. Note the comparative uniformity of response to each injection, with the return of the muscle action potential to about 75 per cent of its control value within seven to ten minutes after each injection.

of the amounts of succinyldicholine given intra-arterially as described above, the recovery of the muscle action potential following stimulation had reached about 50 per cent of its normal value at six minutes, at which time it was noted that different frequencies of stimulation produced responses of different magnitude: stimulation at 0.1-sec. intervals gave a muscle action potential that was consistently higher than that given by stimulation at either 0.05-sec. or 0.25-sec. intervals. Repeated stimulation then resulted in definite fatigue and recovery was not complete until 30 minutes after the succinylmonocholine injection. Secondly, after intra-arterial succinylmonocholine in the same dosage, an intravenous injection of succinyldicholine (0.06 mg./kg.) produced weakness for 20 minutes in contrast to the 11 minutes produced previously by this dose of succinyldicholine alone. When the intravenous succinyldicholine was given, fasciculations were noted only in the limb that had not been subjected to the previous intra-arterial dose of succinylmonocholine.

The most evident effect of choline was recorded in an experiment in which a dose of succinyldicholine was administered intravenously (.25 mg./kg.), followed by choline administered intra-arterially (1.25 mg./kg.), and then, finally, the

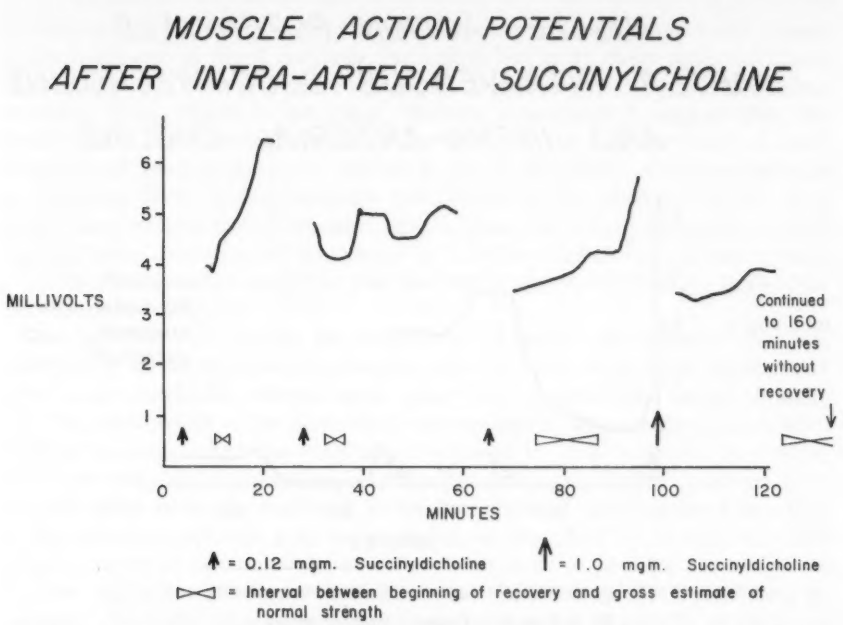

FIGURE 3. Effect of intermittent intra-arterial doses of succinyldicholine (0.05 mg./kg.) on the muscle action potential of tibialis anticus of the cat. Note the increasing time interval between beginning of recovery and gross estimate of normal strength, and the very prolonged effect of a large (1 mg.) dose. See text.

first dose of succinyldicholine was repeated intravenously (Fig. 4). The choline produced a gradual, though not marked, decrease of the recorded muscle action potential; and at the same time a marked fatigue-ability was evidenced, such that stimulation had to be abandoned for approximately 10 minutes. The final dose of succinylcholine was associated with an exceedingly slow recovery: at the end of 32 minutes there was but the faintest of muscle twitches detectable in response to stimulation, and the muscle action potential was correspondingly small.

DISCUSSION

Two features of the action of succinyldicholine and its hydrolysis products are suggested by these admittedly brief investigations.

First, these studies would be most compatible with the view that the intensity and duration of paralysis following succinyldicholine administration is more closely related to the maximum concentration to which the neuromuscular junction is exposed than to the over-all amount of relaxant administered. This would apply only when the total dose is low enough not to create a dual block, with all of the latter's uncertainties as to duration. The intensity and duration of

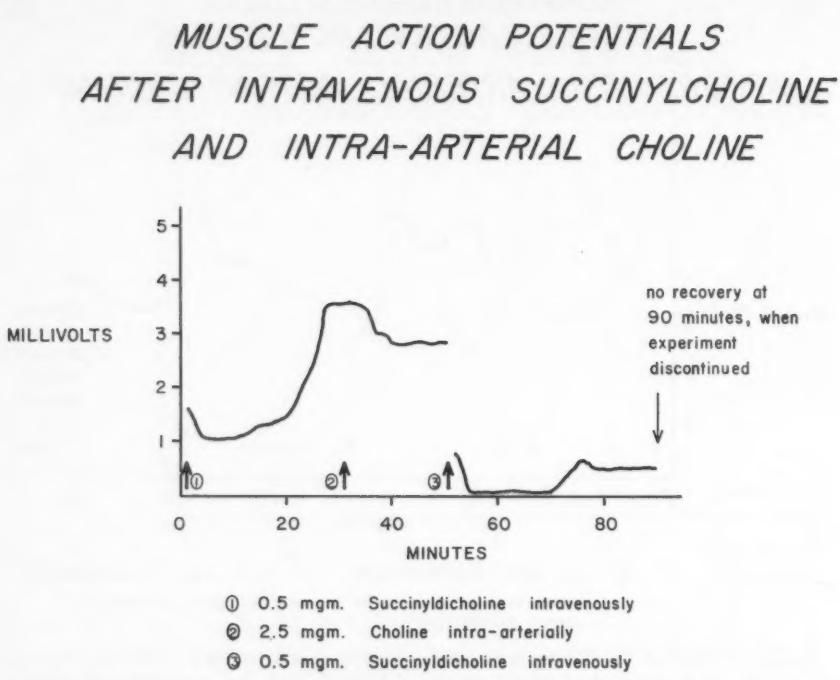

FIGURE 4. Effect of an intra-arterial dose of choline (1.25 mg./kg.) following an intravenous dose of succinyldicholine (0.25 mg./kg.), and its profound effect on a subsequent repetition of the intravenous dose of succinylcholine. See text.

muscle paralysis was markedly greater after intra-arterial injection than after the use of the same dose intravenously. It has been shown by the use of radioactive tracers, that iodocholinium, a muscle relaxant of the depolarizing type, is bound at or near the endplate.[20] It is worth noting in this regard that it is the choline moiety of iodocholinium which is detected as "bound" to the endplate region, and perhaps even to the muscle fibre itself.

Second, although choline chloride, when given intra-arterially in these experiments, in a dose of 1.25 mg./kg. to a fresh animal, produced no effect dependable enough to warrant description, nevertheless, when either choline or succinylmonocholine was given intra-arterially and then succinyldicholine was given, there was a delayed recovery and evidence of fatigue on repeated stimulation.

This phenomenon may have its clinical counterpart in the patient who, after succinyldicholine administration, shows a strong cough at extubation and yet is unable to sustain adequate respirations in the face of even slight respiratory obstruction. The succinylmoncholine or choline would, in such an instance, be derived from hydrolysis of the succinyldicholine that had been administered. It also raises a question as to the validity of the estimation of muscle strength from the tidal volume of unobstructed respiration. It would seem that the most

striking action of the intra-arterial administration of choline in these experiments is not one of direct paralysis, but rather lies in its effect upon the action of a subsequent dose of succinyldicholine. The mechanism by which choline produces these effects is not clear. Hutter's experiments[15] suggest that the facilitation of neuromuscular transmission following the administration of small intra-arterial doses of choline in the cat is due to the ability of choline to cause an elevation of the resting endplate potential from the normal —90 mv. to a figure closer to zero, and at the same time to lower the critical potential at which depolarization becomes self-sustaining to a value slightly nearer the resting potential. The net effect might be that less depolarization is necessary to produce a twitch in such a fibre.

One hypothesis to explain the mechanism of action of choline is that this substance is bound to the endplate region, where it has a weak initial depolarizing action and occupies the receptor areas upon which acetylcholine would normally act. This could result in the blockade of neuromuscular transmission, and is what appears to occur when the endplate is exposed to large amounts of choline. When the endplate is exposed to lower concentrations of choline (perhaps those concentrations normally produced in the hydrolysis of acetylcholine) an effect on the muscle membrane may be produced, as described by Hutter, in which a lesser degree of additional deplorization is required to produce a muscle contraction, and hence either exactly balances out the blocking effect, producing no normally detectable change in transmission from nerve to muscle, or produces an actual facilitation. The fact that choline possesses the property of curare reversal,[15] in the cat at least, would appear to support this hypothesis, for the curare molecules may prevent choline from exerting its blocking effect and its facilitating effect is then predominant.

Summary

In view of experimental work that has pointed to an effect of choline at the neuromuscular junction, and in view of the release of this chemical in the circu'atory bed and tissue spaces upon hydrolysis of succinyldicholine, experiments have been conducted to investigate the possible interaction of choline with succinyldicholine.

The experimental conditions obtained were not sufficiently accurate to warrant conclusions as regards the action of choline directly, and the reader is referred to the detailed and careful studies carried out by Hutter[15] in England and Grob, Johns, and Harvey in Baltimore[14,16] on the action of choline. A marked interaction between choline and subsequently administered succinyldicholine was noted, however, and a hypothesis for the mechanism of action of choline under such circumstances has been presented.

The release of choline by hydrolysis of succinyldicholine and succinylmonocholine is suggested as one cause for prolongation of neuromuscular block during clinical anaesthetic administration of succinylcholine.

Résumé

A la suite de l'administration de doses cliniques de succinylcholine, on a observé un certain nombre de cas de paralysie musculaire prolongée dont les

uns ont été mis sur le compte d'un déséquilibre électrolytique, les autres, d'un déséquilibre acide-base, d'une cachexie, d'une fonction rénale perturbée,ou encore d'une activité anormale de la cholinestérase. Nous savons maintenant que la succinylmonocholine, un des produits d'hydrolyse de la succinylcholine est elle-même un myorésolutif dont l'action est plus faible mais plus prolongée que son précurseur. Nous savons aussi que la choline, un autre produit de l'hydrolyse de la succinylcholine (aussi bien que la succinylmonocholine) peut produire un effet à la jonction myoneurale, et c'est pour étudier l'interaction de la choline et de la succinylcholine que nous avons entrepris cette étude.

A la suite d'injections intra-veineuses et intra-artérielles de succinylcholine et d'injections intra-artérielles de chlorure de choline, nous avons enrégistré les potentiels d'action musculaire par des électrodes sur le tibialis anticus du chat. Nous avons démontré que l'effet myorésolutif de la succinylcholine était plus prononcé lorsque la choline est présente à la jonction myoneurale (à la suite d'injection intra-artérielle de choline).

La libération de choline par l'hydrolyse de la succinylcholine et la succinylmonocholine sont, nous en avons l'impression, une cause de la prolongation du blocage neuromusculaire, lorsque l'on se sert de la succinylcholine au cours de l'anesthésie.

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EXPERIMENTAL STUDIES ON THE FATE OF DECAMETHONIUM*

B. Giovanella, C. Manni, P. Mazzoni, and G. Moricca†

The differences between the mode of action of lepto- and pachy-curares are as yet poorly understood. Among the various obscure points still awaiting a convincing explanation, a most important one is, in our opinion, that related to the manner in which a lepto-curare, after its pharmacological action, is released from the myoneural junction. It is well known that, while the more complex substances such as pachy-curares usually induce long-lasting paralysis, the lepto-curares, which have a simpler structure, exert a shorter muscle relaxant effect. No conclusive explanation for this has been given, at least regarding the methonium salts.

Now, if we admit that the active group in the case of both lepto- and pachy-curares is the quaternary ammonium, as generally admitted, it seems reasonable to assume that the shorter duration of muscle paralysis may be due to the fact that simpler substances are chemically degraded and more promptly inactivated than more complex compounds.

This hypothesis has been experimentally confirmed by several authors[1, 2, 3, 4, 5] in the case of succinylcholine (succinyldicholine). This drug does in fact exert a short duration of action (not more than a few minutes), which is strictly dependent upon the high rate of hydrolysis by cholinesterase. The prevailing view with respect to methonium salts, on the other hand, is that they are released unchanged from the endplate, and even excreted unchanged[6, 7] as happens for the pachy-curares. This hypothesis is based chiefly on the experimental evidence given by Zaimis,[8] who by means of the ammonium reineckate precipitation method has shown that pentamethonium is excreted unchanged into the urine after its intravenous administration. Pentamethonium, however, exerts low curarizing activity, whereas its higher homologue, decamethonium, which exerts marked muscle relaxant properties, cannot be adequately estimated by the use of such method. The data obtained by Zaimis with pentamethonium cannot therefore be directly applied to its higher homologues, except on a purely tentative basis. To acquire further information in this field we undertook a series of investigations with the aim of finding more sensitive chemical or physical methods for the detection of methonium salts. Thus we have been able to develop a specific turbidimetric procedure[9] and we have shown that with this method it is possible to estimate amounts of methonium salts of the order of 5 μg., while with the previous method, as the reineckate reaction, it was not possible to detect less than 10 mg. On the other hand, by means of a radioisotope technique using C^{14}

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labelled C_{10}, we have quantitatively determined the distribution of decamethonium in the animal body.[10] In the present paper, we discuss the results of further observations in which the curve of decamethonium blood concentration levels has been investigated under different experimental conditions.

Material and Methods

The decamethonium (C_{10}) used in our experiments was decamethonium bromide with methyl groups uniformly labelled with C^{14}. The hot synthesis of the compound was performed at the Radiochemical Centre, Amersham, England. The sample employed was 99 per cent pure, and had a 5 μC/mg. activity.

Wistar rats, 200–300 gm. in body weight, received the required amount of decamethonium by intravenous injection. At suitable time intervals, 0.1 ml. blood samples were withdrawn from the femoral vein, and desiccated on aluminum discs. Radioactivity measurements were carried out using a thin window (1.5 mg./cm.^{2}) Geiger counter with lead shield. An E.K.C.O. Scaler Mod. 530A was used for counts over 1000 sec. In some of the experiments the contractions of the faradically stimulated masseter muscle were graphically recorded. At higher doses of decamethonium, when apnoea occurred, tracheotomy was done. Into the trachea of the animal was inserted a plastic tube connected with an automatic respirator supplying a flow of pure oxygen at a pressure of 2 cm. of water and at the rate of 20–30 respirations per min.

Results

The pattern of blood radioactivity following intravenous injection of different amounts of C^{14} labelled decamethonium is shown in Figure 1. Two peaks are present; the first one occurring immediately after the injection and the second one after 20–25 minutes. The second peak corresponds to the beginning of the decurarization phase (shown by the first arrow, while the second arrow shows the end of decurarization). The pattern is almost identical in all of the four curves, the first peak appearing to be proportional to injected amounts only in the three lower curves. The lower curve was obtained following administration of half of the minimal paralyzing dose to a rat; the upper curve was obtained following injection of an amount greater than the paralyzing dose. It is interesting to note that blood concentration levels of intravenously injected d-tubocurarine decrease continuously from the maximum level attained shortly after administration, whereas the decamethonium blood concentration curve shows a second peak occurring at the very beginning of the decurarization phase. This second peak would indeed remain inexplicable, should we accept the classical view that C_{10}, like d-tubocurarine, is released as such from the endplate. If such an assumption is correct, increased blood levels of the active compound should result in enhanced muscle relaxant effect instead of its end. Nor, on the other hand, can it be argued that "desensitization" of the endplate might have taken place, since if more decamethonium is injected at the time of decurarization, a new "paralysis" immediately occurs. The second peak must therefore be caused by a substance containing the carbon atoms of the original methyl groups of C_{10}, which are the carriers of radioactivity, but not by the whole decamethonium molecule. In

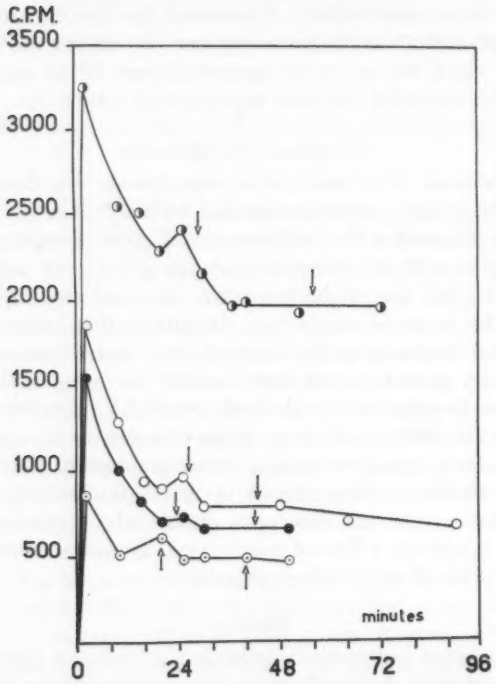

FIGURE 1. ⊙–⊙ 1,2 mg./kg.; ●–● 1,8 mg./kg.; ○–○ 2,0 mg./kg.; ◑–◑ 2,8 mg./kg. intravenously injected decamethonium labelled with C^{14}.

addition, the drop in d-tubocurarine blood content occurs much earlier than that observed with decamethonium; thus, only 15 per cent of the injected amount of d-tubocurarine is still present in blood 40 minutes after injection, whereas more than 33 per cent of the original dose of decamethonium was found to be present after an equal period of time. This finding suggests that d-tubocurarine is eliminated through the kidney and/or the liver much more rapidly than decamethonium, although the latter's action is of much shorter duration, thus providing further evidence in support, even indirectly, of our view.

It seems reasonable to assume that decamethonium, which is slowly eliminated, should maintain muscle paralysis for a longer time than d-tubocurarine, if both drugs, in their active form, are released from the endplate into the bloodstream. On the other hand, if C_{10} is inactivated by the endplate, the presence of an inactive derivate in the blood would not affect the course of "paralysis."

Another feature of some interest lies in the fact that, while the first peak varies depending on the injected dose, the second peak is always nearly the same, irrespective of the dosage employed. In this connection, it should be pointed out that the amount of drug we used in all of the experiments ranged from one-half to a whole paralysing dose. If the degree of paralysis is regarded as the expression

of the number of specific effectors blocked at the myoneural junction, as many as 50 to 100 per cent of them may be considered to have been blocked in the course of our experiments. Accordingly, it is reasonable to assume that the larger the number of effectors blocked, the greater should be the amount of inactivated C_{10} being re-introduced into the bloodstream; but, also, that the higher the initial decamethonium blood levels, the greater the number of effectors thus blocked. Now, the second peak is in absolute value highest when the initial injected dose is elevated, whereas its relative value (i.e., the amount of decamethonium re-introduced into bloodstream minus the decamethonium amount already present in the blood) is practically constant. The relationship between the second decrease in decamethonium blood levels and decurarization may be better understood if we observe Figure 2. In this figure two different graphs are reported: one

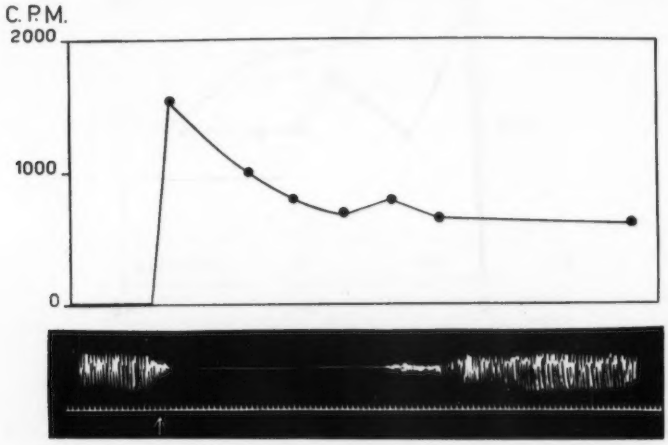

FIGURE 2. ●–● 1,8 mg./kg. intravenously injected decamethonium labelled with C^{14}.

has been obtained by recording the contractions of the faradically stimulated masseter muscle of a rat treated with C_{10}; the other has been obtained by plotting the radioactivity as a function of the time. Since the time units are the same in both measurements, it is clear that the first rise in level of radioactivity corresponds to the onset of paralysis, whereas the second one begins shortly before recovery of muscle excitability.

An additional experiment was carried out to further clarify our hypothesis. One-half the paralysing dose of non-labelled decamethonium was injected first, and an equal dose of radioactive decamethonium was again injected after three minutes. The data obtained are reported in Figure 3, where it may be seen that in the animal pre-treated with non-labelled C_{10} the initial peak is much higher than in the control animal. This is most likely to be due to the fact that non-labelled decamethonium has been fixed by the endplate, thus preventing the fixation of the radioactive compound. Afterwards a decrease of the radioactivity

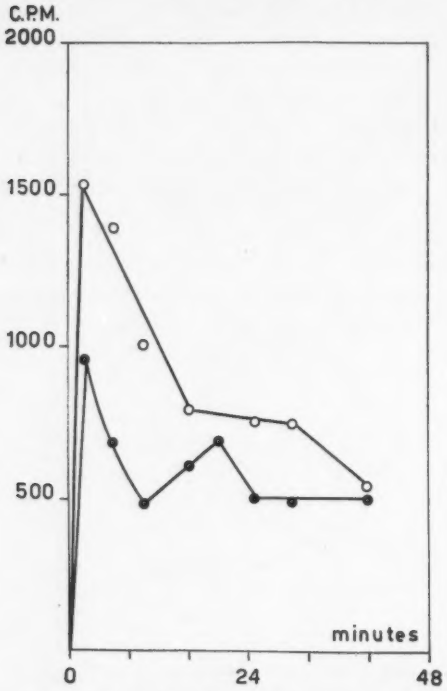

FIGURE 3. ●–● 1,2 mg./kg. intravenously injected decamethonium labelled with C^{14}; ○–○ 1,2 mg./kg. intravenously injected decamethonium labelled with C^{14} 3′ after the injection of an equal amount of non-labelled C_{10}.

appears, and it is followed by a plateau corresponding to the second peak in the control animal. The presence of this plateau is probably the result of superimposition of two curves displaced in three minutes; that is to say, the lapse of time between the first and the second decamethonium injection.

If d-tubocurarine is first administered, and followed after seven minutes by injection of labelled decamethonium, the pattern of blood radioactivity is the same as that obtained from the control animal treated only with an equal amount of C^{14}–labelled C_{10} (Fig. 4). The curve, however, is markedly displaced upwards, with respect to the control, as an effect of injection of a higher dose. It seems, therefore, that both decamethonium and d-tubocurarine act on the same structures, or at least that both compounds are taken up by the same receptors, as shown by the fact that d-tubocurarine injection is followed by a decreased decamethonium uptake. Moreover, it is clear that the mode of elimination of d-tubocurarine differs from that of C_{10}, inasmuch as pre-administration of d-tubocurarine does not modify the decamethonium elimination pattern.

In order to get a more complete picture, it was thought of interest to investigate the pattern of blood radioactivity, following intramuscular injection of C^{14}

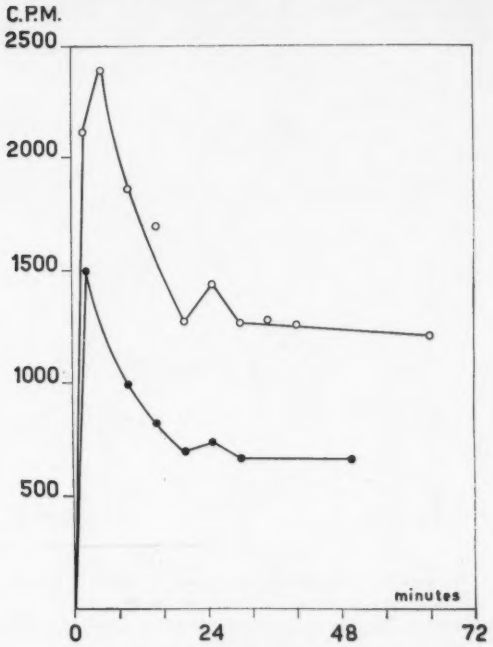

FIGURE 4. O–O 1,8 mg./kg. intravenously injected decamethonium labelled with C^{14}, 7′ after the injection of 0,1 mg./kg. of d-tubocurarine; ●–● 1,8 mg./kg. intravenously injected decamethonium labelled with C^{14}.

labelled C_{10}. The results thus obtained are shown in Figure 5. The typical upper curve was obtained after intravenous injection, the lower curve after an intramuscular injection. As shown by Paton and Zaimis[7] the intramuscular injection is two to three times less effective than the intravenous one and causes a much slower induction of paralysis. In the curve obtained after the intramuscular injection, on the other hand, there is a progressive rise of radioactivity up to the sixtieth minute, followed by a slow decrease. After intramuscular injection in rats there occurred a slight curarization between the thirtieth and sixtieth minute.

To explain the difference in decamethonium blood levels after intravenous or intramuscular administration, it should be recalled that, while in the first instance the whole of the drug is immediately introduced into the bloodstream, with the latter the drug goes into the blood gradually. We believe that, of the two peaks occurring in the case of intravenous injection at the beginning and at the end of curarization, respectively, the first might be tentatively explained as the effect of introduction of C_{10} into the bloodstream, and the second to the release of an inactive degradation product of the drug from muscles, where it is mainly stored. Further support to such hypothesis is given by the data obtained after the intramuscular injection. In this case, the first peak (corresponding to the introduction

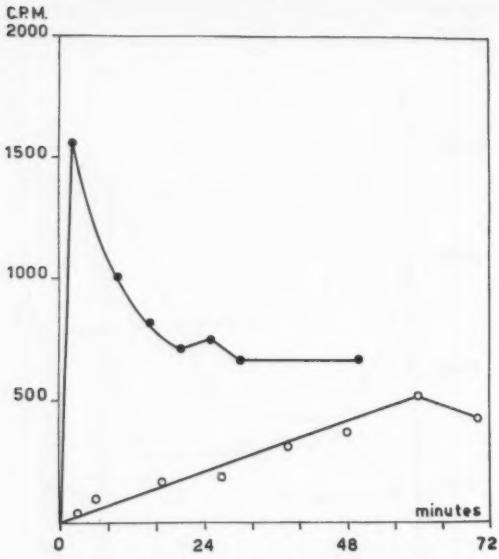

FIGURE 5. O–O 4,1 mg./kg. intramuscularly injected decamethonium labelled with C^{14}; ●–● 1,8 mg./kg. intravenously injected decamethonium labelled with C^{14}.

of radioactive material into the bloodstream) is not present and is replaced by a slow increase in blood concentration levels, as decamethonium is being gradually released into the bloodstream, whereas a peak occurs corresponding to the beginning of the decurarization phase. This phase actually begins at a level of blood redioactivity much higher than that coinciding with the beginning of curarization. This level will be reached much later after the animal has been completely decurarized for several minutes. The only possible explanation for this finding appears to be that only part of the radioactivity is due to the whole decamethonium molecule, the rest of it being caused by an inactive fragment of the same molecule.

CONCLUSIONS

The results of the present study thus provide fairly comprehensive evidence of the fact that decamethonium is inactivated by the endplate, while it seems no more admissible that this drug behaves in a manner similar to d-tubocurarine.

Our findings support the view that decamethonium, following introduction into the bloodstream, becomes fixed by the endplates, where it undergoes degradation which leads to the loss of its pharmacological properties. In this connection, it should be emphasized that the second rise in blood radioactivity following intravenous injection of labelled decamethonium, which corresponds with the beginning of the decurarization phase, cannot be regarded as being due to an active curarizing substance. Also, the subsequent pattern of the curve, if compared to

that previously obtained by other workers with d-tubocurarine, cannot possibly agree with the view that decamethonium is released from the endplate unchanged and thereafter pharmacologically active. It has, in fact, been observed that, although the length of action of this drug is approximately half of that of d-tubocurarine, decamethonium blood levels are maintained for a much longer period of time. An additional point which strongly supports our view is the prompt decurarization of animals treated with C_{10}, in contrast to the slow and gradual recovery of muscle activity noted in those treated with d-tubocurarine. The behaviour of this latter drug is clearly that of a substance which is not fixed in any part of the body and whose effects are merely dependent on the rate of elimination through the kidney or liver. On the other hand, indirect evidence suggests that elimination of decamethonium is likely similar to that of succinylcholine, which is degraded both in blood and muscles by cholinesterase, thus accounting for its extremely short duration of action.

In the case of decamethonium, we have a type of pharmacological action which is intermediate between that of d-tubocurarine and that of succinylcholine. In view of its pharmacological behaviour, and on the basis of our findings, it seems most likely that inactivation of decamethonium occurs at the myoneural junction. In a previous paper,[10] we have shown that when decamethonium blood levels decrease, the drug is accumulated in muscles. When it is re-introduced into the bloodstream, decurarization begins: this fact obviously proves that the drug is released from muscle as an inactivated derivative. The second rise in blood radioactivity corresponds to the release of C_{10} from muscles. The evidence discussed herein indirectly supports the view we have offered. Direct confirmation will be provided only by identification of the compound which is responsible for the second rise in blood radioactivity, or at least by demonstration that it is not identical with C_{10}. Research is now in progress with the aim of developing a new chromatographic procedure for isolation and detection of methonium salts with different length of molecule, and we hope this may be of help in explaining a part of this fascinating problem.

Summary

The decamethonium blood concentration pattern following intravenous injection of C^{14} labelled C_{10} is characterized by two well-distinguished peaks, the first occurring at the time of injection, and the second after variable periods of time, depending on the dosage employed. Thus, the second peak was found to shift from 20–30 min. after injection when the administered dose was increased from 1.8 to 3.0 mg./kg., its time of onset fairly closely coinciding with the initial stage of decurarization, as shown by parallel experiments using graphic recording of faradically stimulated masseter contractions. Based on these findings, and from previous studies by the same workers, an attempt was made to elucidate the causes for the unusual behaviour of C_{10} as compared to d-tubocurarine—the latter, as is well known, exhibiting a simple elimination curve with but one initial peak followed by gradual decrease of blood concentration levels.

Pre-treatment with a large dose of non-labelled decamethonium (5 mg./kg.) results in disappearance of the second peak, which is replaced by an extended

"plateau," whereas pre-treatment with 100 mg./kg. d-tubocurarine causes displacement of both peaks towards the right. The evidence thus substantiates the authors' previously suggested opinion that the initial drop of decamethonium blood levels is associated with its fixation by muscle receptors, and that the second peak, corresponding to the decurarization stage, is due to re-introduction of either inactivated decamethonium or its radioactive degradation products from the muscles into the bloodstream.

Finally, the identity of receptors for decamethonium and d-tubocurarine is discussed.

Résumé

La courbe de la concentration sanguine au décaméthonium à la suite de l'injection intraveineuse de C^{14} marqué C_{10} est caractérisée par deux pics bien distincts le premier survenant immédiatement après l'injection, et le deuxième après des délais variables selon la dose employée. Ainsi, nous avons réalisé que le deuxième pic se déplace de 20 à 30 minutes après l'injection, lorsque nous augmentons la dose de 1.8 à 3.0 mg./kg.; le moment de son début coincide à très peu près avec la phase initiale de décurarisation, comme le prouvent des expériences parallèles où l'on a fait un graphique des contractions des masseters stimulés par un courant faradique. Forts de ces données et à la suite d'autres études par les auteurs, nous avons étudié les causes des effets différents du C_{10} et de la d-tubocurarine, cette dernière, on le sait, donne une courbe d'élimination ordinaire ne montrant qu'un pic suivi d'une diminution graduelle des taux de concentration dans le sang.

Un traitement préalable avec une grosse dose de décaméthonium non marqué (5 mg./kg.) a entraîné la disparition du deuxième pic a été remplacé par un plateau prolongé, alors qu'un traitement préalable avec 100 mg./kg. de d-tubocurarine a entraîné le déplacement des deux pics vers la droite.

Ces faits confirment l'opinion émise au préalable par les auteurs que la première diminution des taux décaméthonium dans le sang est liée à sa fixation par les récepteurs musculaires, et, que le second pic, survenant à la phase de décurarisation, est dû à l'apparition dans le courant sanguin soit du décaméthonium inactivé, soit de ses produits radioactifs dégradés par les muscles.

Finalement, nous discutons de l'identité de récepteurs pour le décaméthonium et la d-tubocurarine.

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THE PREVENTION OF SHOCK FOLLOWING EXTRACORPOREAL CIRCULATION AND HYPOTHERMIA*

WALTER ZINGG, M.D.†‡

THE TITLE of this paper promises more than it keeps. We cannot define "shock": its treatment is to some extent controversial as we know very little about the changes produced by extracorporeal circulation and less about hypothermia. This presentation is nothing but another variation of the old theme: "How to keep the patient alive" or "How to get away with it."

Extracorporeal circulation and hypothermia are two of the most formidable procedures to which patients are regularly submitted. It certainly would have been in order to investigate thoroughly the many rather complicated aspects before employing them clinically. However, the pressing needs of the patients have led to an early and successful clinical application. Although a good deal of work has been done during recent years our knowledge is still very limited and we are really only beginning to understand these processes. The surgeons and their associates, the anaesthesiologists, have entered the experimental field comparatively recently. It is a great disadvantage that so few physiologists, biochemists, and other basic scientists take an active part in the investigation of these problems.

At the Winnipeg Children's Hospital and at the Winnipeg General Hospital, a Kay-Cross Disc Oxygenator is used for all clinical by-pass procedures as manufactured by Pemco. A Pemco heat exchanger is added when the operation is done under hypothermia. The blood is collected in the venous reservoir by gravity and two roller-type pumps are used as arterial pump and coronary sinus suction pump. Everybody knows that the heart-lung machines work well and it has been stated repeatedly that the running of these machines does not present any problems. It is futile to discuss the advantages and disadvantages of the various types of machines. They all work well if they are run properly. However, at the end of the procedure, the man in charge of the by-pass should not be content to turn off his machine, see that the patient's own heart is beating and excuse himself. In the development of shock something may happen which is not immediately apparent but which leads to the shock syndrome and perhaps to death. If this picture develops postoperatively and provided there is no obvious other explanation, such as evidence of myocardial infarction,[1] it must be assumed that the derangement has occurred during the by-pass. Evidently the operator of the machine is very interested in the events during the postoperative phase.

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The following breakdown is an attempt to classify the areas where changes may occur which eventually may lead to shock.

Extracorporeal Circulation

Operation and anaesthesia	Hypothermia
Massive transfusion	Blood flow
Pump, filters, tubing, etc.	Blood balance
Oxygenator	

Of course, postoperative shock can occur without by-pass or hypothermia. The massive transfusion has some inherent dangers which cannot be discussed in this paper. The mechanical parts of the heart-lung machines are always inferior to their living counterparts. The oxygenator may efficiently exchange oxygen and CO_2 but after a moment's reflection it will become evident that it cannot replace the intricate functions of a living lung. In this connection the status of the patient's own lungs during by-pass also has to be considered. Hypothermia is the part which is least understood and the last two items represent the two variables of each individual run.

For this audience there is no need to stress the importance of good anaesthesia, but a few facts regarding the anaesthesia in experimental animals should be pointed out. The experimental work in cardiovascular surgery is mainly done on dogs, and our present knowledge to a large extent is based on observations made on dogs. There are many differences between dogs and humans and great care has to be exercised when applying to patients conclusions based on dog experiments. For convenience sake the most popular anaesthesia for dogs is intravenous pentobarbital. This type of anaesthesia has little in common with modern clinical anaesthesia. Any time we look at results obtained in dogs under these circumstances we should remind ourselves that these results have been obtained in a hypoxic hypercapnic dog under pentobarbital anaesthesia, a situation quite different from a patient anaesthetized in the operating room.

For instance, the acute syndrome of apparently sudden death in the postoperative period following prolonged hypotension, as described by Kirklin, McGoon, Patrick, and Theye,[2] was frequently observed in dogs but not in human patients. The type of anaesthesia may be a contributory factor.

The problems involved in massive transfusions would merit a more detailed description but this is outside the scope of this paper. Several recent investigations have shown that the blood which is in the machine before by-pass has several undesirable properties. It has a low pH and a low sugar content. In the local organization the blood is collected during the previous day by the Red Cross and delivered to the hospitals where it is kept at a low temperature. The blood is preserved in siliconized bottles containing 20 mg. heparin in 30 c.c. saline per 500 c.c. blood. Since the low blood sugar and the low pH are caused by the metabolic activity of the erythrocytes, the blood is kept in the refrigerator as long as possible. It is added to the machine only a few minutes before by-pass. If the heat exchanger is used, the blood is not heated before being added to the machine and if the heat exchanger is not used it is warmed in a water bath to 25° C.–30° C. immediately prior to use. By keeping the period of time during which the blood is at or near body temperature to a minimum it is possible to avoid severe

alterations in the blood. In Table I our findings are compared with those reported in the literature.[3, 4]

TABLE I

DATA IN THE BLOOD USED FOR EXTRACORPOREAL CIRCULATION PRIOR TO USE OBTAINED BY THREE INDEPENDENT GROUPS

	Heparinized blood stored 24 hours			
	Houston		Montreal	Winnipeg
	18 mg* SG†, (4 units)	20 mg. PB‡ (11 units)	18 mg. PB (25 patients)	20 mg. SG (9 patients)
Plasma haemoglobin (mg.%)	20	40	—	35
pH	7.33	7.16	7.27	7.29
Glucose (mh.%)	50	65	—	51
pCO_2 (mm. Hg)	—	—	47.3	40.9
Bicarbonate (mM./L.)	23	23	20.4	18.4

*Mg. of heparin per 500 ml. blood.
†SG = in siliconized glass bottle.
‡PB = in plastic bag.

For the purpose of this discussion, the heart-lung machine is divided into two parts—the oxygenator and the rest, consisting of pumps, reservoirs, filters, connectors, and tubing. The early workers in this field devoted much time and energy to investigations of the mechanical parts of the machines. In order to decrease the damaging effects of rough and wettable materials, the blood comes in direct contact only with plastics, latex, and siliconized highly polished metal. Excessive haemolysis occurs mainly in the coronary sinus suction system. The increased haemolysis is evidenced by an increase of plasma haemoglobin after prolonged periods of by-pass. Although in a clinical case it is impossible to differeniate between the effects of the coronary sinus suction and of the other parts of the machine, there is no doubt that the highest values were found in cases with a high flow through the coronary sinus suction, for a prolonged period of time. In this situation it may be better to lose some blood into the ordinary suction apparatus provided the surgeon's vision can still be maintained.

The liberated haemoglobin is bound to a plasma protein, the haptoglobin, up to a concentration of about 100 mg. per 100 gm.[5] Only the free haemoglobin, that is the plasma haemoglobin in excess of 100 mg. per 100 gm. passes through the renal glomerulus and may lead to renal changes. Free haemoglobin is known to be a powerful vasoconstrictor. It is well known that the finding of a high plasma haemoglobin is associated with a high mortality, but it is difficult to establish a causal relationship since in these difficult and long cases other complications may be present as well.

All pumps produce a pulsatile flow, the characteristics of the pulsations being different in the various types of pumps. Some pumps apparently produce a rather high, short systolic peak which has led to the addition of various devices commonly referred to as depulsators. They usually consist of a membrane or an elastic tube which dampens the peak. With the two roller pumps used in our system, pressures exceeding the physiological range of systolic pressures do not

occur in the patient and we did not find it necessary to introduce depulsators. The rationale is as follows: high systolic pulse peak pressures during by-pass may lead to an excessive stimulation of the carotid body. At the end of the by-pass when the patient's own heart takes over again, this stimulation is terminated but the exhausted carotid body is unable to function properly and a period of hypotension follows. Although another Canadian team has found that in dogs postoperative hypotension did not occur any more following the introduction of a depulsator,[6] a direct experimental proof of this attractive theory is lacking. None of the presently available pumps is ideal except perhaps the McCabe pump which can duplicate the pulse waves exactly, but their performance is adequate for short perfusions.

The same thing can be said regarding the oxygenators. Provided an oxygenator of the right size is used an adequate oxygenation of the blood can always be achieved. A few years ago the possible dangers of over-oxygenation attracted a great deal of attention, especially if there is a temperature gradient between oxygenator and patient. Since this problem could not be solved by experiments it became a matter of beliefs, and, as it often happens there are now two groups, the believers and the non-believers. Since the believers could not prove their point, one of their spokesmen resorted to a nice diplomatic trick. He pointed out that over-oxygenation must be assumed to be dangerous and therefore it would be up to the non-believers to prove that it is innocuous.[7] Of course, this negative proof is much more difficult to furnish. This problem cannot be fully discussed here, suffice it to mention the practice of several groups to use fully oxygenated blood at a temperature of 10° C. or less to induce hypothermia with no ill effects.

The carbon dioxide brings up many rather complicated problems, especially if hypothermia is added to the by-pass. One of the main functions of the anaesthesiologist and of the pump operator is the prevention of alkalosis or acidosis. Derangements of the pH are important factors in the development of postoperative shock.

Whether or not slight and intraoperative changes of the acid-base balance are beneficial is still a controversial problem. Edmark[7] advises the production of a temporary acidosis during hypothermia. Before describing the methods used by our group, I would like to present a small portion of the physiological background. A fall in pH can, of course, be due to a fall of the bicarbonate (metabolic acidosis) or a rise of the pCO_2 (respiratory acidosis). Under hypothermia the normal pH and the pCO_2 change and conversion factors and nomograms have been worked out in order to calculate corrected values. At the lower temperature, more CO_2 is dissolved and consequently the pCO_2 corresponding to the same total CO_2 is lower. However, all workers in this field agree that these factors are quite unreliable. During the last months our group has started to do serial determinations of arterial pH, pCO_2, and bicarbonate during open heart surgery. These determinations can be done expeditiously with the Astrup apparatus. At the present time we are unable to change the temperature of the water bath surrounding the electrode and interpetation of the values obtained at a lower temperature consequently is difficult. For the expression of the data the method described

by Brewin, Gould, Nashat, and Neil[7] was adopted fully realizing, however, that some of the interpretations may be erroneous. If a blood sample is equilibrated with varying CO_2 tensions and the pH determinations are plotted against the CO_2 on semilogarithmic paper, the dots fall on a straight line and this line is independent of temperature. The line is shifted to the left side in acidosis and to the right in alkalosis. During by-pass and hypothermia, the pCO_2 may change due to a variety of reasons. Based on determinations of pH and pCO_2 in the same blood sample, this line has been constructed for each patient. Two representative examples are given in Figures 1 and 2.

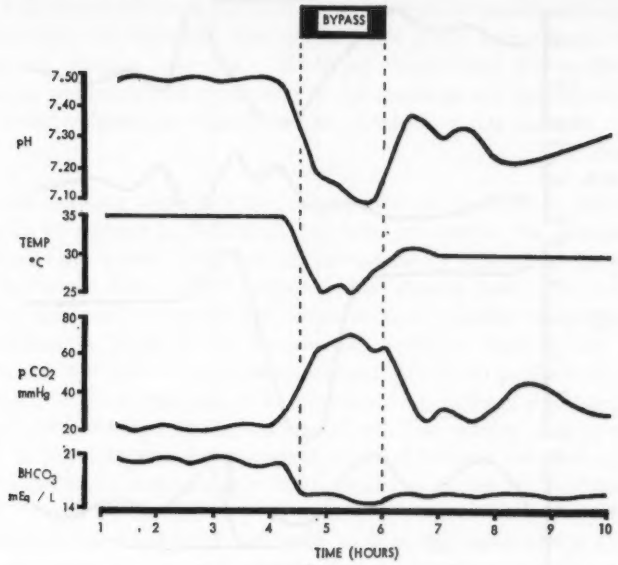
Regarding blood flow there is not much to be added. Although low flow rates may be tolerated for short periods of time, the aim is to have a flow of at least 2.3 L./m^2/min. The oxygen saturation of the venous blood is about 75 per cent or more during a perfusion at this rate, and the A-V difference, accordingly, is 25 per cent. At lower flow rates the A-V difference increases. If bloodstream cooling is used, it must be realized that large areas of the body mass are cooled slowly and remain at a temperature higher than the one recorded in the oesophagus. The oxygen requirements are therefore higher than those calculated on the basis of a single temperature reading. Whereas it is permissible to start the cooling on partial by-pass, it is necessary to complete the cooling period on total by-pass. During partial by-pass the upper parts of the body are perfused with warm blood pumped by the heart. The rectal temperature at this time may be lower than the oesophageal temperature. The brain probably is cooled adequately only during the period of total by-pass.

Finally, the question of blood balance. During and immediately after the by-pass a reasonably accurate blood balance must be maintained. All the reservoirs of the machine are calibrated and the operator knows at all times how much blood has been added to, or removed, from the patient's circulation. The blood loss is estimated by the conventional methods. As a final check at the end of the by-pass, the blood is drained from the machine and measured exactly. The amount of blood transfused can then be accurately calculated.

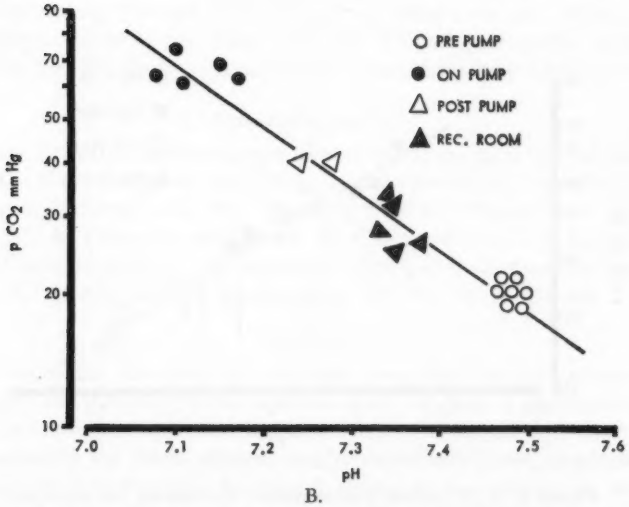
At the end of the operation the patient should have the physiological circulatory blood volume. This, however, may be different from the preoperative circulating blood volume in view of the surgical corrections which have been made. The weight of the patient is therefore of very limited value, inasmuch as weight changes do not reflect these alterations and also do not provide information regarding internal haemorrhage or fluid shifts between the various compartments.

From the practical standpoint the venous pressure determination provides the best index of the adequacy of the circulating blood volume.

Our experience has confirmed the impression of others that a moderate over-transfusion is beneficial. At the end of by-pass the patient is transfused until the venous pressure rises 2–5 cm. The majority of patients require only 200–300 c.c. which, incidentally, is the quantity of normal saline present in the machine blood. It is not an over-transfusion. Patients who underwent total correction of tetralogy of Fallot may require over-loading of 500 c.c. and more, which may lead to a temporary rise in venous pressure up to 20 cm. of water. As we have gained more experience we have been increasing the amount of blood transfused more



A.



B.

FIGURE 1. A 21-year-old male patient. Complete correction of tetralogy of Fallot. A. Oesophageal temperature, pH, pCO_2, and bicarbonate (uncorrected) plotted against time. Note the metabolic acidosis during by-pass and hypothermia with partial correction at the end of the operation and in the recovery room. Patient made an uneventful recovery. B. The pCO_2 and pH determined in the same blood sample are plotted on semilogarithmic paper.

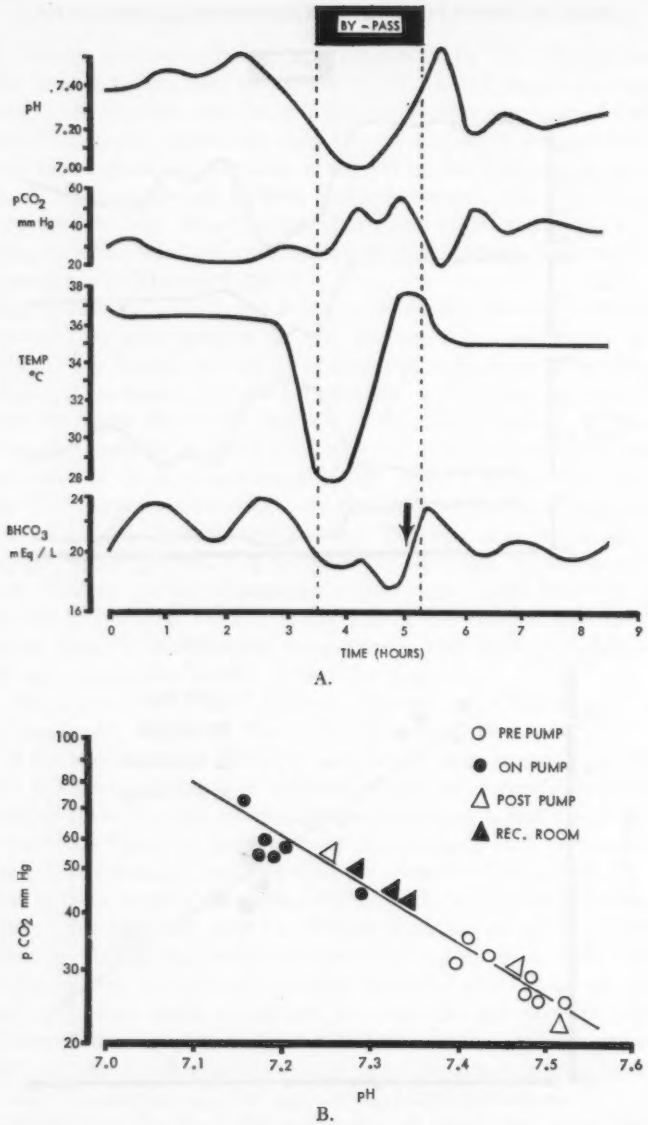


FIGURE 2. A 36 year-old female patient. Cardiotomy for aneurysm of the sinus of Valsalva. A. Oesophageal temperature, uncorrected pH, pCO_2 and bicarbonate recorded from the beginning of the operation until patient arrived in recovery room. Note metabolic acidosis during by-pass and hypothermia with a further fall in bicarbonate when temperature returned to normal levels. At the arrow 40 mEq. of sodium bicarbonate were given intravenously resulting in a rise of the bicarbonate and pH. B. pH and pCO_2 plotted on semilogarithmic paper.

and more. I do not think we have ever caused harm by over-transfusion, but in several early cases we regretted that we had not given more blood. Should an over-transfusion actually take place, the heart dilates and the venous pressure rises. Since the patient is still connected to the machine via the venous catheters the excess blood volume can then be removed within a few seconds.

Summary

The current thinking regarding the management of patients on the heart-lung machine, with or without hypothermia, has been reviewed. The following points appear to be of importance for a smooth postoperative phase and the prevention of shock: adequate flow; slight hypervolemia during and after by-pass and hypothermia; minimal use of coronary sinus suction; possible temporary acidosis during hypothermia. Some of our theories are based on facts, others are based on fantasies and will have to be reviewed again. The main problem is to provide enough oxygen to the living cells and to remove CO_2 without upsetting the acid-base balance and other physiological equilibria. The trouble is that we do not know what is physiological for a patient on total by-pass whose lungs are not perfused, whose major organs are at 25° C. and the rest of the body somewhere between 27° C. and 34° C.

Many problems have not been discussed, such as the value of the EEG, which usually shows severe changes at the beginning of partial by-pass. These problems are actively investigated in many centres and as time goes on we shall get a better understanding. I would like to close by quoting a remark which a member of the audience made to me some time ago following a similar presentation: "If you know so little about your subject it is surprising how much you can do."

Acknowledgments

The author gratefully acknowledges the excellent co-operation of the cardiac surgeons, Dr. C. C. Ferguson and Dr. L. L. Whytehead, of the anaesthetists at the Winnipeg Children's and the Winnipeg General Hospitals, of the cardiologists, Dr. G. R. Cumming and Dr. T. E. Cuddy, and of the respiratologists, Dr. R. M. Cherniak and Dr. M. Lertzman. The gas determinations were done by Mr. E. F. Smith, and the photography by Mr. D. A. Gibson.

Résumé

Nous avons passé en revue les opinions courantes sur les traitements des malades sous les machines cœur-poumon, avec ou sans hypothermie. Si l'on désire des suites opératoires sans incident et prévenir le choc, il faut surveiller les points suivants: un débit suffisant; une hypervolémie légère, pendant et après la dérivation et l'hypothermie; un emploi minimum du système de succion du sinus coronaire; une acidose temporaire possible durant l'hypothermie.

Un certain nombre de nos théories son basées sur des faits, les autres sont fantaisistes et seront étudiées plus attentivement. Le problème essentiel est de procurer assez d'oxygène aux cellules vivantes et de faire éliminer le CO_2 sans troubler l'équilibre acide-base et les autres équilibres physiologiques. L'ennui provient du fait que nous ne savons pas ce qui est physiologique chez un

malade en dérivation totale dont les poumons ne sont plus perfusés, dont les principaux organes sont à 25° C., et le reste du corps quelque part entre 27° C. et 34° C.

Si un choc s'amorce au cours de la période postopératoire à la suite d'une dérivation, et qu'on ne trouve pas d'autres causes apparentes, tel un infarctus du myocarde, on peut présumer que le choc est attribuable à la circulation extracorporelle. Il faut éviter que le sang se détériore au cours de la conservation.

Une grande quantité d'hemoglobine plasmatique libre semble nuisible; l'hémolyse survient surtout dans le système de succion du sinus coronaire.

Il est toujours possible d'oxygéner 100 per cent avec l'oxygénateur. Au cours de l'hypothermie, il n'est pas facile de préciser la concentration du CO_2. Tel que l'ont proposé Brewin, Gould, Nashat, et Neil, nous avons présenté les résultats sur un papier semilogarithmique.

Nous avons observé que, à la fin de l'opération, un léger excès de transfusion peut être avantageux.

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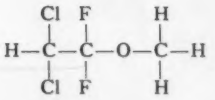
METHOXYFLURANE (PENTHRANE): A LABORATORY AND CLINICAL STUDY*

GORDON M. WYANT, F.F.A.R.C.S., CHUNG AI CHANG, M.D., D.P.H. (TOR.), AND EMANUELE RAPICAVOLI, M.D.

METHOXYFLURANE is one in a series of fluorinated compounds which have been studied in recent years to determine their usefulness as anaesthetic agents. Of the many such substances synthetized only few have been sufficiently promising to warrant clinical trials in man; methoxyflurane is one of those.

Chemical and Physical Properties

Methoxyflurane is 2,2 dichloro-1, 1-difluoro ethyl methyl ether, with the following structural structure:



It is a clear, colourless liquid with a strong sweetish odour. Its boiling point is 104.8° C. at 760 mm. Hg pressure which is unusually high for an inhalation anaesthetic agent and it has a specific gravity of 1.4224 at 25° C. At room temperature methoxyflurane is non-flammable in anaesthetic concentrations. Flash point is 63° C. and oil/water coefficient of 1 per cent methoxyflurane is 400. Depending upon the vaporizer, a maximum of 4 per cent methoxyflurane can be vaporized during clinical anaesthesia.[1]

EXPERIMENTAL STUDY

Following a number of pilot studies the effects of methoxyflurane were studied on five healthy unpremedicated male volunteers using our previously published method of investigating the cardiovascular effects of anaesthetic agents in man.[2]

During a series of pilot studies it had become evident that in these fit unpremedicated individuals induction with methoxyflurane-oxygen alone or with nitrous oxide-oxygen-methoxyflurane was difficult and time consuming, and in some instances impossible using a standard no. 8 Heidbrink vaporizer with wick. It was further found that if anaesthesia was induced with sodium thiopental and endotracheal intubation done under succinylcholine, it was usually not possible to vaporize sufficient methoxyflurane in oxygen to maintain anaesthesia, once the thiopental had worn off. It became evident, therefore, that nitrous oxide-oxygen-methoxyflurane had to be used for some time after induction before the nitrous

*Generous supplies of methoxyflurane (Penthrane®) were made available through the courtesy of Dr. P. Nash of Abbott Laboratories, Montreal, P.Q. who also assisted with a Grant-in-aid.

†From the Department of Anaesthesia, University of Saskatchewan and Department of Anaesthesia University Hospital, Saskatoon, Saskatchewan.

oxide could be discontinued. In order to maintain anaesthesia, it was necessary to place three vaporizers, two of them no. 10 Heidbrink type with wicks, in series and having them all in the full-on position (Fig. 1). Attempts at mainte-

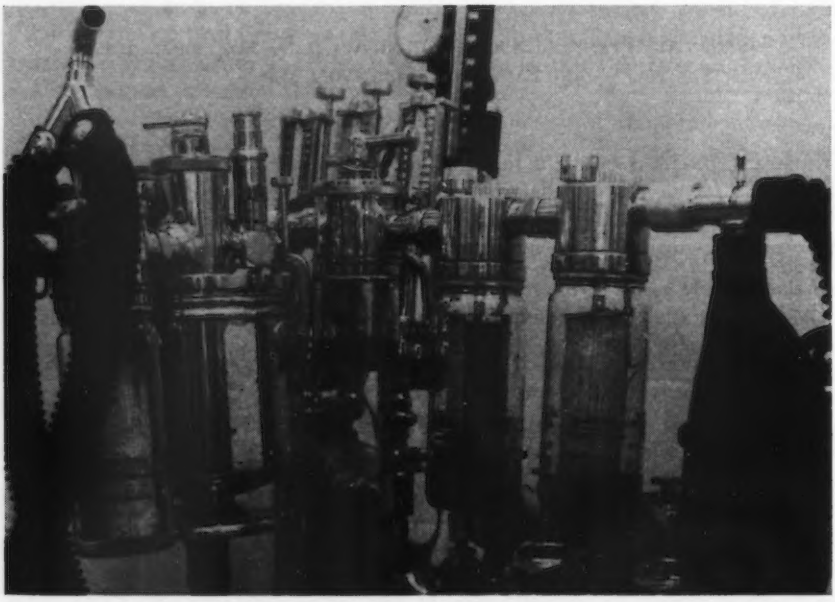


FIGURE 1. Heidbrink Anaesthetic Machine showing three vaporizers in series for administration of methoxyflurane to volunteers.

nance of anaesthesia in a closed-circle system with the vaporizer on the expiratory side had to be abandoned because the low gas flow made it impossible to vaporize sufficient methoxyflurane to compensate for losses so that the individuals gradually woke up. It must be emphasized, however, that no tests were done with copper-kettle type vaporizers.

Consequently, the method employed in our studies was one of thiopental induction followed by endotracheal intubation under succinylcholine with previous topical anaesthesia to larynx and trachea with 4 per cent lidocaine. Anaesthesia was then maintained with a high flow of nitrous oxide-oxygen and methoxyflurane, the nitrous oxide being discontinued when possible, but usually not before 10 to 15 minutes. After a further 10 minutes of stable anaesthesia with spontaneous respiration, cardiac output was measured and peripheral and pulmonary blood pressures were recorded. Also at that time arterial blood samples were withdrawn from the femoral artery for blood gas determinations. Thereafter, controlled respiration by means of an Etsten hand ventilator was instituted for 10 minutes, and all measurements repeated. Anaesthesia was then discontinued, the subject was allowed to awaken and all parameters were again measured on recovery.

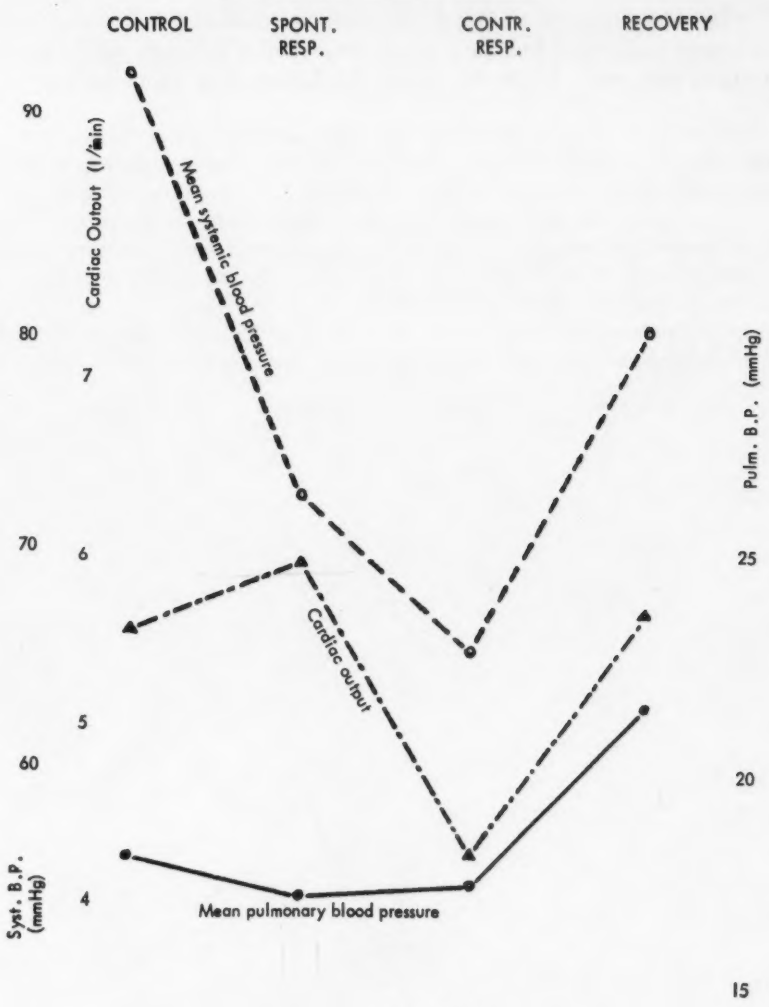


FIGURE 2

Systemic blood pressure (*Fig. 2*). There was a sharp drop of mean systemic blood pressure from 92 to 72 mm. Hg during methoxyflurane anaesthesia and spontaneous respiration. A further drop to 65 mm. Hg occurred with controlled respiration. These changes were statistically valid and occurred in all individuals. On recovery there was a return of mean systemic blood pressure to 80 mm. Hg.

Pulse-rate. Mean pulse-rate showed little change throughout the experiments, being 71.3/min. for control, 92/min. for both spontaneous and controlled respirations, and 86.6 min. during recovery.

Cardiac output (*Fig. 2*). Little if any change in cardiac output occurred with spontaneous respiration, but there was a drop from 6 to 4.5 L. with controlled respiration and return to pre-anaesthetic levels just prior to awakening. None of these changes were significant.

Stroke volume. This followed closely upon cardiac output being 78.3 ml., 65 ml., 46.1 ml., and 65.7 ml. respectively for the four stages of the experiment.

Pulmonary blood pressure (*Fig. 2*). This did not change significantly during the entire experiment and remained within normal limits throughout.

Total peripheral resistance (*Fig. 3*). Some slight decrease occurred during spontaneous respiration followed by an increase during controlled respiration which was significant. Resistance returned to control values on recovery.

Total pulmonary resistance (*Fig. 3*). This showed no change during spontaneous respiration, but there was a rise during controlled respiration with a fall

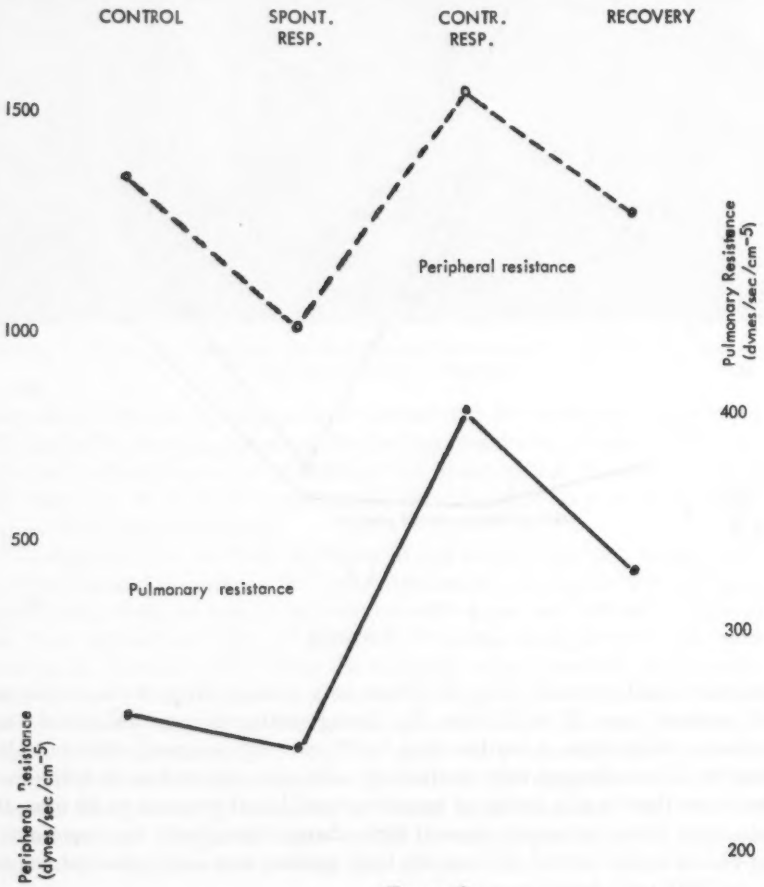


FIGURE 3

towards normal on recovery. However, none of these changes were of statistical significance.

Electrocardiogram. No changes were observed in the electrocardiogram in any of the experiments.

Electroencephalogram. This was not specific but was compatible with light anaesthesia.

Blood gases (*Fig. 4*). A very sharp drop occurred in the pH on spontaneous respiration with a slight recovery during controlled respiration. Equally the pCO_2

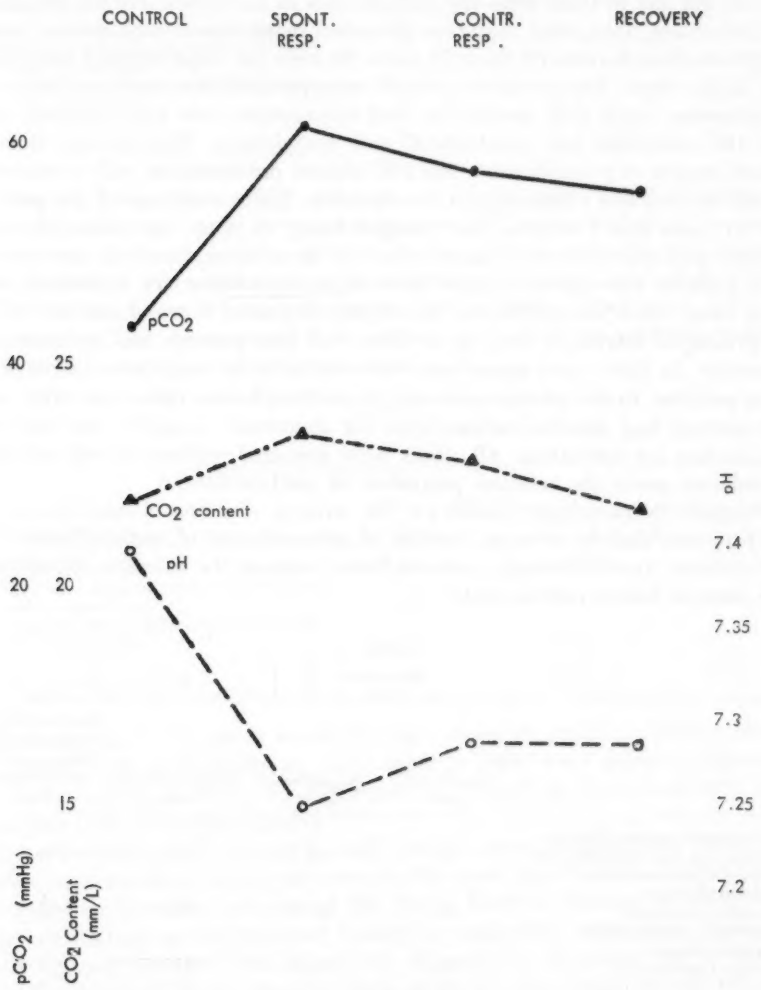


FIGURE 4

rose sharply on spontaneous respiration but only gradually fell off during controlled respiration and recovery. Changes in CO_2 content were insignificant. These findings were in conformity with the clinical observation of powerful respiratory depression by methoxyflurane.

Clinical Study

Methoxyflurane was administered to 89 patients as a supplement to nitrous oxide anaesthesia. All but seven were gynecological procedures. Nitrous oxide-oxygen-methoxyflurane was used both for induction and maintenance 13 times and all but one of these were the earliest cases in this series. For the remaining 76 procedures, thiopental induction preceded maintenance with nitrous oxide-oxygen-methoxyflurane. Of these 76 cases, 63 were for major surgical procedures and 10 for minor. Seventy-seven patients were premedicated with morphine and scopolamine, eight with meperidine and scopolamine, one with atropine only, and the remainder had secobarbital and scopolamine. The average time of administration of premedication was 102 minutes pre-induction with a maximum of 340 minutes and a minimum of nine minutes. The average age of the patients was 41 years and 5 months, the youngest being 13 years, the oldest 76 years. Seventy patients received a muscle relaxant, 56 of them dimethyl-tubocurarine. Nine patients were given a single dose of succinylcholine for intubation only, all in cases which did not involve laparotomy. Repeated doses of succinylcholine for prolonged relaxation were given once, and four patients had gallamine for relaxation. In three cases anaesthesia was reinforced by small intravenous doses of meperidine. In the nitrous oxide-oxygen-methoxyflurane induction series, only two patients had dimethyl-tubocurarine for abdominal relaxation and one succinylcholine for intubation. All others were managed without muscle relaxants in order to assess the relaxant properties of methoxyflurane.

Duration of anaesthesia (*Table I*). The average duration of anaesthesia was 108.1 minutes and the average duration of administration of methoxyflurane was 86.3 minutes. In other words, methoxyflurane was on the average discontinued 21.8 minutes before nitrous oxide.

TABLE I

Duration

	Number of cases	Anaesthesia (min.)	Methoxyflurane (min.)	Methoxyflurane discontinued before end of anaesthesia (min.)
Nitrous oxide-methoxyflurane (induction and maintenance)	13	108.4	89.6	18.8
Thiopental nitrous oxide-methoxyflurane (major operations)	66	119.4	94.6	24.8
Thiopental nitrous oxide-methoxyflurane (minor operations)	10	32.5	27.2	5.3
TOTAL AND AVERAGE	89	108.1	86.3	21.8

Amount of methoxyflurane used (*Table II*). The average amount of methoxyflurane used was 17 ml. per operation or 0.2 ml. per min. of methoxyflurane administration. These figures were higher for those cases in which methoxyflurane induction was used and lower with thiopental induction.

TABLE II
AMOUNT

	Number of cases	Methoxyflurane (ml.)	Methoxy flurane/min. administration
Nitrous oxide-methoxyflurane (induction)	13	28	0.31
Thiopental nitrous oxide-methoxyflurane (major operations)	66	16.7	0.17
Thiopental nitrous oxide-methoxyflurane (minor operations)	10	4.5	0.16
TOTAL AND AVERAGE	89	17	0.2

Wake-up time (*Table III*). Although, as shown above, administration of methoxyflurane was on the average discontinued 21.8 minutes before the end of anaesthesia, the average wake-up time after anaesthesia was still 36.6 minutes, or 59.1 minutes after methoxyflurane had been discontinued. Again these figures were higher where nitrous-oxide-oxygen-methoxyflurane was used both for induction and for maintenance of anaesthesia and could be markedly reduced by using thiopental as the induction agent.

TABLE III
WAKE-UP TIME

	Number of cases	Postoperative (min.)	Post-methoxyflurane (min.)
Nitrous oxide-methoxyflurane (induction)	13	54.6	73.8
Thiopental nitrous oxide-methoxyflurane (major operations)	66	35.1	60.9
Thiopental nitrous oxide-methoxyflurane (minor operations)	10	22.8	27.8
TOTAL AND AVERAGE	89	36.6	59.1

In order not to prejudice results by early cases in which experience had to be gained with methoxyflurane, cases done in 1960 were analysed separately from those done in 1961. No difference was noted in these and they have therefore been presented together.

Complications. Both operative and postoperative complications were few. Severe hypotension occurred only once in this series and this was easily reversed by reducing the concentration of the drug. Reduced minute volume was a common finding and necessitated assisted or controlled respiration. Postoperatively apnoea occurred three times and on only two occasions did it respond to anticholesterase drugs. Since in these, as in all other cases, muscle relaxants

had been used sparingly, this condition was no doubt due to the potentiating effect between methoxyflurane and the non-depolarizing muscle relaxants. The third apnoea must have been due to the respiratory depressant effect of methoxyflurane itself and resolved spontaneously after a period on the respirator. Really severe postoperative nausea and emesis occurred only once in this series and in this respect methoxyflurane compared very favourably with other agents.

Discussion

The *experiments on volunteers* proved that methoxyflurane caused some hypotension, but in the presence of a reasonably well maintained cardiac output, stroke volume, and total peripheral resistance this was not of very great significance.

Effect of methoxyflurane on the pulmonary circulation was negligible. The absence of electrocardiographic changes was quite striking. In unpremedicated persons it is quite difficult to maintain anaesthesia with methoxyflurane using standard vaporizers with wicks, because of the high boiling point and the difficulty in obtaining adequate concentrations of the drug. Much more striking than the cardiovascular effects was the marked respiratory depression caused by the drug. This was evidenced by changes in pH and pCO_2 when the subjects were allowed to breathe spontaneously for any length of time. Clinically also there was marked reduction of tidal volume. This effect on the respiration is not too significant as long as it is remembered that at least assisted or, probably better, controlled respiration must be used with methoxyflurane.

The most striking impression gained from the *clinical use* of methoxyflurane was the apparent unpredictability of wakening time after administration of this agent. Even if administration had been discontinued a good time before the operation ended, the patient often still continued to sleep for quite a long period of time after relatively small amounts of the drug had been exhibited, when in other cases the patient awoke almost immediately after a very much larger dose. These results bear no clear relationship to duration of administration, age, or any similar factors which commonly influence wakening time after anaesthesia. However, recovery time was usually shorter in obese patients, all else being equal. This was exemplified in the following two instances.

The longest wake-up time after discontinuing methoxyflurane was 235 minutes and followed gastrectomy in a 51-year-old man who was 67½ inches tall and weighed 162 pounds. The duration of methoxyflurane administration was 165 minutes, it having been discontinued 50 minutes before the end of anaesthesia. The amount of the drug administered in a semiclosed system with high nitrous oxide-oxygen flows was 30 ml. In contrast the patient who had received the largest amount of methoxyflurane, namely 60 ml., woke up within 50 minutes of the end of administration of the drug. This was a 36-year-old woman, 62½ inches tall and obese with a body weight of 153 pounds. She underwent tuboplasty and uterine suspension which involved 190 minutes of anaesthesia with methoxyflurane discontinued 20 minutes before end of anaesthesia.

This curious phenomenon can be explained by the observation of Chenoweth[3] that methoxyflurane concentration tends to increase in the fatty deposits of dogs even after administration of this drug has been discontinued and the animals

begin to awaken. Thus the blood level of methoxyflurane falls more rapidly if the agent can escape into abundant fatty deposits while being exhaled at the same time. In lean individuals, fall of blood concentrations is largely dependent upon pulmonary elimination only and awakening is consequently slower. Hence the apparent paradox that in the lean person administration must be tapered off even earlier than in the obese, which is contrary to experience with other anaesthetic agents. While slow awakening is not necessarily a great handicap where good postoperative supervision is available, it could be significant when no postoperative observation area is available.

Methoxyflurane is not easily adaptable to the changing needs for different depths of anaesthesia, as it takes some time to deepen anaesthesia and even longer to reverse undue depth. Thus methoxyflurane lacks a degree of flexibility.

On the positive side of the ledger, on the other hand, is the small incidence of operative and postoperative complications and the fact that the difficulty in volatilizing the drug implies a certain safety factor which must not be easily overlooked.

Induction with nitrous oxide-oxygen-methoxyflurane is a relatively slow process and can hardly ever be accomplished in under five minutes. Induction and also maintenance with methoxyflurane are easier and less of the drug is required if patients are adequately premedicated.

Muscle relaxation with methoxyflurane is quite adequate for lower abdominal operations. However, since this involves the administration of somewhat larger concentrations with further delay in wakening, it is better to use small doses of muscle relaxants and thus decrease the amount of methoxyflurane required. Furthermore, hypotension may be caused by attempting to produce profound muscle relaxation with methoxyflurane.

Summary and Conclusion

Methoxyflurane is a new fluorinated and chlorinated saturated asymmetrical ether whose outstanding physical properties are an unusually high boiling point and the fact that it is non-flammable in anaesthetic concentrations.

Its greatest usefulness seems to lie in its role as an adjuvant to nitrous oxide anaesthesia. Methoxyflurane is a potent respiratory depressant but has relatively little effect on the cardiovascular system. Profound hypotension will occur with undue depth of anaesthesia but changes in the electrocardiogram have not been observed.

Methoxyflurane lacks a certain degree of flexibility as far as ready changes in depth of anaesthesia are concerned and on occasion recovery from anaesthesia is quite markedly delayed. There is some evidence that the drug concentration increases in the adipose tissue after administration has been discontinued, thus accelerating the lowering of plasma levels in the obese patient and decreasing wakening time. Since it is a rather long-acting agent, administration should be discontinued well before the end of operation and concentrations should be tapered off even earlier.

Methoxyflurane is capable of producing a degree of abdominal muscle relaxation but it is recommended that small doses of muscle relaxants be used in order

to reduce the amount of methoxyflurane required. The agent enhances the effect of the non-depolarizing muscle relaxants. Although induction of anaesthesia with nitrous oxide-oxygen-methoxyflurane is possible and is not unpleasant, it is slow, implies the use of more methoxyflurane, and is undesirable from the point of view of awakening. It is therefore recommended that anaesthesia be induced with intravenous barbiturates and adequate premedication is desirable.

Administration of a nitrous oxide-oxygen-methoxyflurane sequence was accompanied by few operative and postoperative complications and in that regard the drug compared favourably with other anaesthetic techniques.

Résumé

Nous avons étudié le méthoxyflurane dans des conditions précises chez des volontaires mâles en bonne santé sous prémédication en employant notre méthode, publiée antérieurement, pour l'étude des effets cardiovasculaires des agents anesthésiques chez l'homme. Suivant cette procédure, nous avons soumis 89 malades à l'anesthésie.

Le méthoxyflurane est un nouvel éther asymétrique saturé, fluriné, et chloriné. Ses propriétés physiques étonnantes sont: un point d'ébullition extraordinairement élevé et son inflammabilité en concentrations anesthésiques.

Sa plus grande utilité consiste à servir d'adjuvant au cours de l'anesthésie au protoxyde d'azote. Le méthoxyflurane est un puissant dépresseur de la respiration, mais il ne produit que peu d'effet sur le système cardiovasculaire. Si l'anesthésie est poussée à une profondeur inaccoutumée, il s'ensuivra une hypotension marquée, sans qu'il soit possible toutefois de dépister des changements électrocardiographiques.

Le mythoxyflurane manque de flexibilité si l'on désire des changements dans la profoundeur de l'anesthésie, et il pourra arriver que le réveil soit plutôt tardif.

Il semblerait que ce médicament s'accumule dans la graisse après que l'administration a cessé, produisant ainsi un abaissement des taux dans le plasma des obèses et hâtant le réveil.

Etant donné que le méthoxyflurane produit des effets prolongés, il faut arrêter son administration longtemps avant la fin de l'opération, et il faut diminuer les concentrations encore plus antérieurement.

Le méthoxyflurane peut produire un certain relâchement des muscles abdominaux, mais il est préférable de donner de petites doses de curarisants dans le but de réduire la quantité de méthoxyflurane requise. Cet agent augmente l'effet des myorésolutifs non dépolarisants.

Bien que l'induction de l'anesthésie avec un mélange de protoxide d'azote, oxygène et méthoxyflurane soit possible et ne présente rien de déplaisant, cette induction est lente, nécessite une plus grande quantité de méthoxyflurane et, si l'on songe au réveil, on ne peut pas la conseiller. On conseille plutôt une induction avec des barbituriques par voie endoveineuse, et une bonne prémédication est de mise.

L'administration d'un mélange de protoxide d'azote, oxygène et méthoxyflurane pour maintenir l'anesthésie n'a été suivie que de peu de complications opératoires ou post-opératoires, et sous cet angle-là, le méthoxyflurane se compare avantageusement avec les autres techniques anesthésiques.

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McGILL UNIVERSITY EXPERIENCES WITH METHOXYFLURANE*

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THIS REPORT covers preliminary studies with methoxyflurane from hospitals connected with the Department of Anaesthesia at McGill University. When the department was presented with this new anaesthetic agent, evidence of its over-all safety was available from animal and clinical studies. A clinical report had indicated that the anaesthetic features were a fair reflection of the physical properties.[1]

The Department at McGill decided that it would be of benefit to estimate the clinical usefulness of the agent under ordinary working conditions in each hospital. Specific features of the agent might merit more detailed examination at a later date. The total number of cases being small—314—it was realized that any opinions formed were the result of clinical impressions and unlikely to stand up to statistical analysis. Each of five groups of anaesthetists answered seven questions and an attempt to embody the replies is made in this paper.

The operations may be classified by site as follows:

Intracranial	7
Intrathoracic (lungs)	18
Abdominal	65
Oropharangeal	38
Perineal	22
Orthopaedic (including spine)	47
Peripheral Structures (trunk and limbs)	117
TOTAL	314

The age distribution of the patients was four months to 83 years. The weight distribution was 17½ lbs. to 224 lbs. The longest duration of operation was seven hours.

The first question the investigators were asked was, *"Can the agent be used in conventional apparatus*?" The ether vaporizer on the Boyle's machine was used with satisfaction in all the hospitals. One hospital replaced the ether bottle by the trilene bottle for this purpose. The usual practice was to open the tap fully and then to vary the concentration by raising or depressing the plunger. The highest concentration reported was 2.9 per cent when 7 L. of gas were bubbled through the agent per minute, with the ether bottle in place. With the plunger fully raised concentrations as low as 0.5 per cent were found at this flow. One anaesthetist used a gas flow of 4 L. per min. through this apparatus with satisfaction. Another used a Heidbrink wick ether vaporizer. With this vaporizer com-

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pletely open concentrations of 1.6 per cent could be obtained. Another group used the agent with the Vernitrol vaporizer. With a 1,500-c.c. oxygen flow through the vaporizer they obtained a 3 per cent concentration. This was diluted to any desired concentration by adding gases from the by-pass. All these concentrations are approximate. In the vast majority of cases the gas flow from these vaporizers was fed into a circle absorption semiclosed system. In a few cases a non-return system was used, and occasionally the Magill attachment of the Boyle's machine. All these methods of administration were considered satisfactory. In 15 cases the agent was administered in a closed Coxeter-Mushin absorber system. No measurements of concentration were obtained here, but it was noted that condensation of water on the agent in the vaporizer appeared to seal it off.

The second question asked was, "*Are there any dangers or contra-indications to this agent*?" It was agreed by all groups that hypotension *might* occur. However, the degree of hypotension experienced by each group varied greatly. All groups reported falls in systolic blood pressure of 20 mm. Hg as being not unusual. In nine cases, falls greater than this were reported, the greatest being a seventy mm. drop, from 160 to 90, when the patient was manually ventilated with 2 per cent methoxyflurane. In only two other cases were drops greater than 50 mm. recorded and in none of these three cases did the systolic blood pressure fall below 90 mm. Hg.

Slight bradycardia was common, but none severe enough to need atropine. One patient developed extrasystoles after 25 minutes of 0.8 per cent methoxyflurane. The rhythm did not revert to normal with 0.4 mgm. atropine I.V. and the arrythmia lasted 60 minutes after the agent had been discontinued. One other patient developed extrasystoles in the recovery room.

Operations not requiring relaxation are not associated with undue respiratory depression, but increasing depths of anaesthesia will produce depression to the point of apnoea. Neither laryngeal nor bronchial spasms were reported with the agent. Surgical stimulation in light stages of anaesthesia did not produce laryngeal spasms even if marked limb movements were present. Two diabetics were given the agent and were satisfactorily controlled on their normal insulin requirements. In 22 cases adrenalin was used in combination with the agent without arrythmias.

The third question was, "*What are the characteristics of methoxyflurane as an inducing agent*?" It was agreed by all groups that induction was slow with methoxyflurane; generally at least 15 minutes were required before an adequate state of anaesthesia was attained. The vapour did seem to be non-irritant and rapid increases in concentration were possible without producing coughing or laryngospasm. Relaxation of the jaw muscles occurs early but the tracheal reflexes are much more slowly obtunded. Laryngeal irritability disappears early and once adequate surgical anaesthesia has been reached hurried intubation is unnecessary.

The fourth question was, "*Is it best used alone or in combination*?" It was generally agreed that the slowness of the agent as a substance for induction is best overcome by using thipentone or nitrous oxide. Maintenance with methoxyflurane alone is satisfactory but the addition of nitrous oxide was preferred.

The fifth question was, *"What are the relaxation characteristics of the agent?"* Adequate abdominal relaxation could be produced at the expense of respiration, but control of respiration was greatly facilitated by methoxyflurane. One group reported no hypotension with curare. Three groups reported that in six out of nine cases where the agents were used together, there was hypotension of 20 mm. Hg or more. The greatest drop was 60 mm. Hg from 150 to 90 mm. when 9 mg. of d-tubocurarine was given to a patient receiving 1 per cent methoxyflurane. This was immediately corrected by the administration of 0.4 mg. of atropine. Methedrine was also reported to correct such hypotension. One group felt that there was no potentiation of d-tubocurarine, but two groups considered that potentiation did occur. Two groups reported a mild fall in blood pressure with gallamine. It was undecided if there was potentiation of this drug. All groups agreed that with succinylcholine there was neither potentiation nor fall in blood pressure.

The sixth question was, *"What are the maintenance characteristics of this agent?"* The general opinion was that, providing a satisfactory level of anaesthesia is attained, fluctuations in depth do not occur rapidly. It is possible to maintain smooth anaesthesia. Where hypotension has occurred it may be corrected by reducing the concentration of the agent without the course of anaesthesia being disturbed. In two cases the agent was abandoned because of undesired hypotension and in two other cases because of unsatisfactory operating conditions.

The seventh question was, *"How do the patients recover?"*

Time. With experience and anticipation of surgical requirements, awakening could be produced at the end of the operation. However, in general, 60 minutes was required for full awakening. Two patients after prolonged operations did not respond to painful stimuli for six to eight hours. Delayed awakening in one other patient will be described separately.

Shivering. Up to 30 per cent of paediatric patients shivered but this was reduced to 10 per cent in adults.

Nausea and vomiting. Nausea occurred in some 20 per cent of patients and vomiting in about 10 per cent.

Postoperative restlessness. This was present in about 14 per cent of cases.

Postoperative analgesia. The relatively prolonged awakening time is associated with a diminished need for narcotics. It was thought possible that this diminution extended into the first 24 hours. One unusual postoperative course is reported in a middle-aged male who had a left hemicolectomy for uncomplicated diverticulitis. The patient developed marked postoperative sodium retention with water diuresis. The latter resembled diabetes insipidus. The patient was unusually drowsy, though responding, for three days. He eventually made a complete recovery.

In conclusion we would point out that methoxyflurane has advantages which will appeal to some anaesthetists or be applicable to certain situations. As yet it would seem to be a safe anaesthetic. The slow induction and awakening may, however, mitigate against its final acceptance in the armamentarium of the anaesthetist.

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BLOOD TRANSFUSION REACTIONS DURING ANAESTHESIA: A CLINICAL STUDY*

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O God! that bread should be so dear,
And Flesh and blood so cheap!
The Song of the Shirt, Thomas Hood (1798–1845)

IT IS the anaesthetists' responsibility to decide whether or not blood is to be given during surgery. That this is indeed a responsible decision may be clearly seen from the following facts: 4.5 million transfusions are given each year in the continental United States. In 1958, one in ten of all hospital patients received blood. Varying reactions occurred in 3 to 5 per cent of those transfused. One death resulted from every 1,000 to 3,000 administrations.[1] From these figures a yearly minimum of 1 500 deaths attributable to this procedure can be estimated. This is an annual mortality higher than that from acute appendicitis.[2]

The anaesthetist should be aware of the problems associated with blood transfusion reactions under anaesthesia, so that morbidity and mortality rates may be reduced.

THE PHYSICO-CHEMICAL COMPOSITION OF STORED CITRATE WHOLE BLOOD

In order to appreciate clinical manifestations of blood transfusion reactions during anaesthesia, an outline of the physico-chemical composition of stored refrigerated citrate whole blood is informative (Table I). A unit of refrigerated citrate whole bank blood contains 120 c.c. of acid citrate dextrose (A-C-D) solution which contains 2.5 gm. di-sodium hydrogen citrate and 3.0 gm. dextrose. The final concentration of citrate is approximately 2 gm./500 ml. unit of blood.[3] The physical characteristics of bank blood when administered are: a temperature between 4°C. and 10°C.,[4] a hematocrit determination between 40 and 60 per cent[5] and a pH of approximately 6.6 to 7.1,[6] a shift of the oxygen dissociation curve to the left,[6] an increase in free hemoglobin[7] and potassium,[8] and a depleted unbound calcium in the plasma.[9] There is a deficiency of platelets, antihemophilic globulin, and the labile factor.[10] The white blood cells are non-functioning.

It is apparent that stored citrate whole blood is not the ideal physiological solution.

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TABLE I

STORED REFRIGERATED CITRATE WHOLE BLOOD (ONE UNIT)

A-C-D	120 c.c.
Citrate	2 gm.
Temperature	4–10° C.
Haematocrit	40–60 per cent
pH	6.6–7.1
O_2 dissociation	shift to left
Free HBG	increased
K^+	increased
Ca^{++} (unbound)	decreased
Platelets	decreased
AHG	decreased
Labile factor	decreased
WBC	non-functioning

DIAGNOSIS AND MANAGEMENT OF BLOOD TRANSFUSION REACTIONS DURING ANAESTHESIA

The incidence of transfusion reactions has been creditably reduced owing to the development of increasingly sensitive methods[11, 12] for cross-matching and better understanding of physico-chemical components. Despite this improvement, however, when reactions do occur they carry an unfortunate morbidity and mortality. This is particularly true for those occurring under general anaesthesia, since recognition and hence management is often delayed because of masked classical clinical presentation. Thus, a variety of blood transfusion reactions continue to occur. This can be appreciated by a perusal of Table II.

TABLE II

BLOOD TRANSFUSION REACTIONS

Early	Late
Most common	transmission of disease
allergic	
pyrogenic	isosensitization
haemolytic	
mechanical	transfusional siderosis
Less common	
biochemical	
hypothermia	
bacterial contamination	
transfusional haemorrhagic diathesis	
legal	

The anaesthetist is concerned primarily with the group of early reactions but should also be aware of the fact that late untoward effects may occur as a result of the transfusion of blood. It is significant that all early reactions may present diagnostic clinical manifestations under anaesthesia. This aspect of these reactions will be emphasized in the following discussion.

Early Reactions

Most common.

ALLERGIC. During anaesthesia these reactions are characterized by wheals and

facial oedema. Severe asthma or anaphylactoid shock are rare under anaesthesia.[3] The cause of most allergic reactions may be on a basis of sensitivity.[13] In most of the mild reactions it is not necessary to halt the administration of blood. An antihistamine such as phenergan, pyribenzamine, benadryl, or chlor-trimeton may be given intravenously. If a more alarming reaction such as bronchial asthma or laryngeal oedema should occur, the emergency treatment of that condition is indicated, using epinephrine, aminophylline, and corticosteroids (Solu-cortef). It may be advisable prior to transfusion to administer an antihistamine to patients with a strong history of allergy, or who have previously experienced allergic reactions to transfusions.[14, 15]

PYROGENIC (FEBRILE) REACTIONS are characterized by chills and fever. This reaction may be described as any temperature rise during anaesthesia considered to be caused by an infusion of blood and unaccompanied by haemolysis. Four main causes are recognized: (i) exogenous (bacterial) pyrogens, mainly in the equipment (use of disposable sets has reduced the incidence of these reactions); (ii) endogenous pyrogens. Recently, several workers have demonstrated the association of febrile reactions with the presence of (iii) leuko and (iv) platelet agglutinins in the recipient's serum.[16] These reactions were demonstrated only in patients who had received multiple transfusions.

This febrile reaction must be accurately differentiated from the more serious haemolytic reaction. Examine the patient's plasma. If it is clear, there has been no significant haemolysis. After a febrile reaction has begun, the administration of aspirin or antihistamines[14] will lessen the intensity and duration of the episode.

HAEMOLYTIC TRANSFUSION REACTION is defined as a reaction accompanying or occasioned by the infusion of blood in which there is a shortening of the survival time of the red cells of the donor or of the recipient. It may result from one of three principal causes: specific antigen-antibody reactions, nonspecific destruction of red cells, faulty administration of blood.

It is pertinent to emphasize that many of the reported fatal haemolytic transfusion reactions have occurred when blood was administered to anaesthetized patients. This seems reason enough in itself for avoiding the practice of giving one bottle of blood during anaesthesia "just in case it is needed".[17] It also indicates the desirability of adequate preparation of the patient with regard to preoperative blood volume replacement and, if possible, delaying the administration of blood until the patient is conscious. If there is severe bleeding during surgery, many units of blood will by necessity be given, but giving a "unit of blood" routinely during an uncomplicated operation is unwarranted and not without risk.

Hypotension, petechiae, unexplained oozing sudden in onset, fever, and tachypnoea are signs of a haemolytic reaction which are not altered by anaesthesia. The bleeding accompanying this type of reaction is caused by marked intravascular clotting. This intravascular clotting results in hypoprothrombinemia and hypofibrinogenemia in addition to the thrombocytopenia which accompanies a haemolytic transfusion reaction.[18, 19] In the majority of case reports[20] of incompatible blood transfusion reactions during anaesthesia, hypotension was by far the most common and frequently was the only sign present. Hypertension was possibly an early manifestation, under general anaesthesia, in one of our patients.

When a blood transfusion is complicated by massive intravascular haemolysis, plasma haemoglobin levels may easily exceed 300 mg./100 ml. At plasma levels above 150 mg./100 ml., haemoglobin will appear in the urine.[3] This haemoglobinuria will continue until the plasma haemoglobin level has fallen to about 75 mg./100 ml. From a practical viewpoint, for the anaesthetist, a visual inspection for plasma haemoglobin is a simple and extraordinarily valuable procedure. Haemoglobin levels of plasma from blood drawn in a standard manner will seldom exceed 5 to 10 mg./100 ml. This concentration is insufficient to be detected by the unaided eye. Levels of 25 mg./100 ml. appear pink in a test tube and levels of 100 mg./100 ml. are red.[3] Thus, any significant haemolysis can be discovered by the simple procedure of prompt inspection of the plasma.

The first step in the treatment of a haemolytic transfusion reaction is to stop the transfusion. Later, intravenous normal saline and corticosteroids may be required.

Fatalities from haemolytic reactions most commonly follow renal damage with anuria. Death may also result from cardiac arrest due to K^+ overload.

The pathogenesis of renal failure following transfusion of incompatible blood has not been satisfactorily explained. Mueller[21, 22] concludes that inasmuch as haemoglobinuria *per se*, hypotension *per se*, and a combination of these two factors seem to be ineffective in consistently producing experimental renal failure, it seems that some other component of the anaphylactic-like reaction to incompatible blood might have an aetiologic relation to the renal disease. Such a component has not as yet been identified.

MECHANICAL DISTURBANCES.

(1) *Circulatory overload reactions.* In normal individuals the intravenous administration of fluids increases blood volume, raises venous and intra-auricular pressures, and increases cardiac output. Patients with reduced cardiac reserve, such as the aged or those with pneumonia, coronary heart disease, and anaemia, are particularly susceptible to circulatory overload reactions, as are patients undergoing pneumonectomy or multiple lobectomy.[23] In these patients the cardiac output may decrease, resulting in hypotension, if blood is given too rapidly or in too large quantities.[24] Acute circulatory failure manifested as pulmonary oedema may be precipitated.[25] Use of packed red cells, clinical observation of the venous pressure, a slow rate of infusion, and placing the recipient in the semi-Fowler position will reduce the likelihood of pulmonary oedema.

(2) *Air embolism.* Blood transfusion under pressure presents a potential source of this complication. Once it occurs, hypotension, tachycardia, cyanosis, and death may result. The mechanism of death is acute right heart failure. The right heart fills with air, and the entrance of blood into the pulmonary circulation through the outflow tract of the right ventricle stops. Diagnosis is made by recognizing the source of the air. Auscultation of the heart reveals the characteristic crunching murmur, often described as a "mill-wheel" murmur. Treatment is by the removal of air from the right ventricle between the second or third ribs to the right of the sternum, with the patient left side down. These manœuvres relieve the cardiac airlock and improve patency of the pulmonary artery.

Less common.

BIOCHEMICAL DISTURBANCES.

(1) *"Citrate intoxication."* There are clinical situations where the controversial "citrate intoxication" might feasibly occur: (i) in the presence of any factor which might impair body metabolism of citrate, for example, cirrhosis of the liver; (ii) hypothermia, where there is a decreased rate of metabolism; (iii) avitaminosis, hypoparathyroidism, and oesteoporosis, where calcium is not mobilized from bone; (iv) in the child or newborn, where there are inadequate calcium stores; (v) in shock, where there is little or no blood supply to bone.

The administration of calcium is the specific therapy. It is estimated that, in the normal adult weighing 60 kg., as much as 2 L. of citrated blood can safely be given in 20 minutes.[4, 5] If more than this is given it would seem wise to inject 10 ml. of 10 per cent calcium gluconate for every litre of citrated blood administered.

(2) *Potassium intoxication.* During the storage of blood the potassium content of the red cells decreases and that of the plasma increases. The normal potassium plasma level of 4 to 5 meq./L. rises to about 20 meq./L. after 14 days storage.[3] In adults with good renal function, potassium toxicity from stored citrated blood probably presents no problem, except in massive blood transfusion. However, when transfusing patients with oliguria or anuria, blood stored for less than two or three days should be utilized whenever possible, since not only does the potassium level of plasma rise during storage, but from older stored blood there is an increased number of red cells broken down on infusion, which adds further potassium load.

HYPOTHERMIA. We have seen this more commonly in the newborn, infant, or child. However, the adult as well as the child, during deliberately induced hypothermia, may have a precipitous drop in temperature by 3° to 5° C. following transfusion of refrigerated stored blood.

BACTERIAL CONTAMINATION. Reactions from infected blood are uncommon. The bacteria are usually cold-growing or psychrophilic Gram-negative pseudomonads, coliforms, or achromobacters which may produce lethal endotoxins. In these reactions there is usually immediate circulatory collapse which responds poorly to emergency measures.[5, 26] Cortisone and levarterenol have been effective in the treatment of these reactions. Confirmation of the cause of the reaction rests mainly on the demonstration of bacteria, in residual blood, as shown by direct smear and by culture.[26]

TRANSFUSIONAL HAEMORRHAGIC DIATHESIS. Clotting defects[4] have been attributed to decreased platelets, decreased ionized calcium, increased plasma citric acid levels, fibrinolysis, decreased labile factor, and hypothermia. The recommended treatment for decreased platelet clotting defect is the administration of fresh drawn blood; for decreased Ac globulin or labile factor, fresh bank blood or lypholized plasma (antihaemophilic plasma); for decrease in fibrinogen, whole blood which contains 250 mg. per cent fibrinogen, or fibrinogen *per se*.

LEGAL. This aspect has been discussed extensively in several recent reviews,[27, 28] and is not to be elaborated upon here.

Late Untoward Effects

Transmission of disease. The most common disease transmitted by transfusion

is homologous serum hepatitis (1 in 200–500 transfusions). Its mortality is reported to be from 0.2 to 10 per cent.[29] No way to sterilize whole blood has yet been found.

Isosensitization. Even with the most careful selection of blood, every transfusion carries a certain risk of inducing isosensitization. The danger of isosensitization increases with the number of transfusions. There is no product available deserving designation as "universally" safe blood, that is, one which can be given without any risk to a patient without preceding pretransfusion test. For this purpose, the routine addition of corticosteroids to blood should be condemned.[30] Admittedly there are surgical situations in which the need for replacement of blood volume is so urgent and critical that no waiting period can be interposed before giving the blood. The anaesthetist requesting this procedure must realize that such a step represents a definite calculated risk. For one, the patient may already have antibodies for the blood administered. At the Vancouver General Hospital, 2 per cent of those patients requiring transfusion have abnormal circulating antibody.[31] In 1 to 2 per cent of cases, the patient may become sensitized as a result of the transfusion.[2] This fact is especially important in the female in childbearing age since it may place in jeopardy the fate of subsequent offspring.

To sum up then, as outlined in Table III, blood transfusion reactions during anaesthesia can be differentiated on the basis of key clinical manifestations and confirmations made by simple laboratory procedures.

TABLE III

DIAGNOSIS OF BLOOD TRANSFUSION REACTIONS DURING ANAESTHESIA

Clinical manifestation	Differential diagnosis	Confirmation
wheal	allergic	
fever	haemolytic	plasma haemoglobin urine haemoglobin direct coombs bilirubin
	pyrogenic	coombs' consumption test
	bacterial contamination	direct smear bacterial culture
petechiae	haemolytic	
unexplained oozing	haemolytic bacterial contamination	
	massive transfusion	coagulogram
hypotension	haemolytic	
	circulatory overload	venous pressure haematocrit blood volume $K^+\uparrow$ citrate $\uparrow$ $NH_3\uparrow$ $Ca^{++}\downarrow$
	bacterial contamination	
	air embolism	auscultation
pulmonary oedema	circulatory overload	
arrhythmia	massive transfusion air embolism haemolytic	ECG, $K^+\uparrow$

Summary

Inescapably the anaesthetist is responsible for the decision as to whether or not blood is to be given during the surgical period. That this decision is, indeed, a responsibility, may be seen by the fact that there is an estimated annual death rate of 1 in 1,000 to 3,000 administrations in the U.S.A. This gives a yearly minimum of 1,500 deaths attributable to blood transfusions in the continental United States alone. Moreover, despite increasingly sensitive methods of cross-matching blood and a better knowledge of physico-chemical factors, a variety of reactions with a 3–5 per cent incidence continue to occur. Unfortunately, they still carry a significant morbidity and mortality rate. Particularly is this true during anaesthesia, where late recognition and management may result because of masked classical clinical presentation. The anaesthetist should be wary when giving blood to patients with any history of previous reaction or known allergies. The more common early reactions are allergic, pyrogenic, haemolytic, and circulatory overload; less common are air embolism, potassium and citrate intoxication, hypothermia, transfusional haemorrhagic diathesis, and bacterial contamination. Late untoward effects of blood can also occur. These are, mainly, transmission of disease, isosensitization, and transfusional siderosis. It is significant that all early blood transfusion reactions present key diagnostic clinical manifestations under anaesthesia. These are readily confirmable by simple laboratory procedures. An awareness of these features of blood transfusion reactions during anaesthesia will lead to their prompt recognition and management, thereby reducing morbidity and preventing mortality.

Résumé

Indiscutablement, l'anesthésiste est responsable de la décision à prendre s'il faut donner ou non du sang durant l'opération. Que cette décision constitue une responsabilité de démontre par le fait que, aux Etats-Unis, le taux annuel des morts est de 1/1000 à 1/3000 transfusions de sang. Cela donne un minimum annuel de 1500 morts attribuables aux transfusions sanguines dans les Etats-Unis continentaux seulement. En dépit de méthodes de plus en plus ensembles pour faire les groupements sanguins et une meilleure connaissance des facteurs physico-chimiques, il survient encore dans 3 à 5% des cas des réactions variées. Malheureusement, elles entraînent un taux important de morbidité et de mortalité. Cela est particulièrement vrai au cours de l'anesthésie, alors que le tableau clinique classique est masqué, et que le diagnostic et le traitement sont retardés. L'anesthésiste doit avoir l'œil ouvert lorsqu'il donne du sang à des malades qui ont une histoire de réactions antérieures ou d'allergies connues. Les réactions précoces les plus fréquentes sont des réactions allergiques, pyrogéniques, hémolytiques et une surcharge circulatoire; les réactions moins fréquentes sont : l'embolie gazeuse, l'intoxication au potassium et au citrate, l'hypothermie, la diathèse hémorragique transfusionnelle, et la contamination bactérienne. Il peut exister également des accidents tardifs. Ils consistent surtout en la transmission de maladie, l'isosensitisation, et la sidérose transfusionnelle. Il faut noter que toutes les réactions précoces aux transfusions, sous anesthésie, présentent des manifestations cliniques clés pour faire un diagnostic. Elles peuvent être confirmées

instantanément par de simples examens de laboratoire. La surveillance de ces signes des réactions transfusionnelles au cours de l'anesthésie va aider au diagnostic et au traitement précoces et réduire ainsi la morbidité, et éviter la mort.

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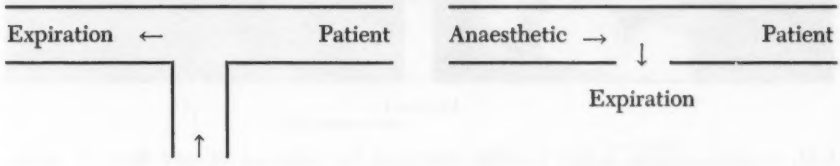
A MODIFICATION OF AYRE'S TECHNIQUE*

AUDREY LEWIS, M.D., AND W. E. SPOEREL, M.D., F.R.C.P.(C.)†

MANY MODIFICATIONS[4] have been described since Ayre published his "T-Piece" technique in 1937.[1] While Ayre emphazises the use of tubing of varying length attached to the expiratory opening of the T-piece, modifications have been employed without such a sidearm or reservoir.[3,8,9,11] The simplest of such modifications is in our opinion a piece of rubber tubing (connecting the gas machine with the endotracheal tube) in which, as close as possible to the endotracheal tube, a hole is cut in order to allow the escape of anaesthetic gases and expired air. In such a system, the flow of gases differs from that in Ayre's T-piece.



For the modified technique we have used a piece of tygon tubing with an internal diameter of 1 cm. and about 4 cm. long, with a side hole of 1 cm. in diameter; this tubing fits tightly the inside of a Foregger connector and can be slipped over a Bird plastic endotracheal adapter (Fig. 1). A piece of non-kinkable endotracheal tube is interposed between the tygon tube and the tubing coming from the anaesthetic machine in order to increase the flexibility. Used with a flexible endotracheal tube, this system can be adapted to any form of surgical drape and has the least bulk and weight possible. The anaesthetic machine can be moved any distance from the patient since the length and diameter of tubing between the expiratory opening and the gas machine is of no significance as long as a sufficient volume of gases can be delivered through it.

For the evaluation of such a system the following factors must be considered: that a concentration of anaesthetic adequate for the maintenance of anaesthesia can be administered; that the resistance is low enough to allow unobstructed breathing; that carbon dioxide is eliminated. In all T-pieces arrangements with a reservoir, the flow of gas must be adjusted to the size of reservoir[7] in order to avoid accummulation of carbon dioxide.

From the above description it is obvious that without a side-arm or reservoir

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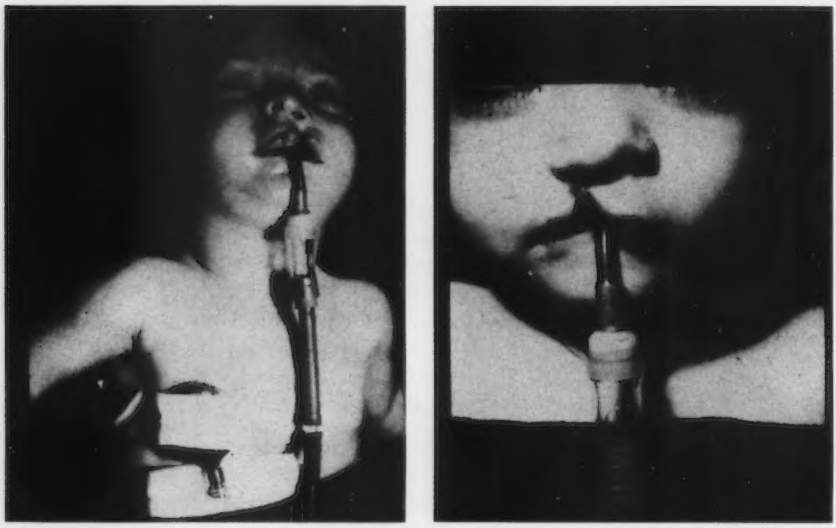

FIGURE 1

CO_2 accummulation is not possible since, in the absence of any flow of anaesthetic gases, the patient will breathe room air through the expiratory opening with practically no added dead space. Thus, the limiting factors of the described modified technique are the resistance to breathing and the maintenance of a satisfactory level of anaesthesia. In order to confirm our clinical impression that this technique is satisfactory and in order to measure the volume of gas flow necessary to obtain an adequate anaesthetic concentration, the following investigations have been carried out.

METHOD

The resistance to flow of the expiratory opening was determined by occluding one end of the tube and connecting the other end to a source of compressed air. The pressure distal to the hole was measured with a strain gauge manometer at flows between 10 and 40 L. per min.

In order to determine the factors influencing the concentration of anaesthetics, the tube was connected to a model lung, consisting of a 10-cm. length of corrugated tubing (representing the trachea) and an empty to-and-fro sodalime canister attached to a Starling pump (representing the lungs). The volume of the model was about 1 L.; ventilation at rates from 10–50 per minute and tidal volumes between 50 ml. and 250 ml. were used. Gas was constantly sampled through a fine plastic tubing placed inside the canister and analysed for its Oxygen tension with a Pauling oxygen analyser (Beckman scale 0–160 mm.). The anaesthetic mixture was represented by nitrogen: in the model the decrease in oxygen tension should be in proportion to the increase of nitrogen, that is, representative of the increase in anaesthetic concentration inside the lung. A

similar system was used by Eger[5] for investigation of the circle system. In our results we shall refer to the percentage of nitrogen attained in the model lung, assuming that this concentration would be of the same order if an anaesthetic gas mixture had been used at the same rate of flow.

With this model, the effects of gas flow, pulmonary ventilation, variation of the diameter of the tube (8, 10, and 12 mm.), and the diameter of the expiratory opening (2–12 mm., tube 10 mm. in diameter) were studied.

Results

If our technique is to be suitable for infants and children, the expiratory peak flow in addition to the inflowing gas mixture must pass through the expiratory opening without an undue increase in pressure inside the tube. Brooks *et al.*[4] reported the resistance of an Ayre's tube of 1 cm. in diameter at a flow rate of 50 L. per min. to be less than 1 cm. of water. Our values including those of a "T-piece" of 7 mm. in diameter were considerably higher (Fig. 2); this could be partly due to different measuring techniques. With an expiratory opening 8 mm. in diameter the resistance appeared to be too high. It was felt that a 10 mm.

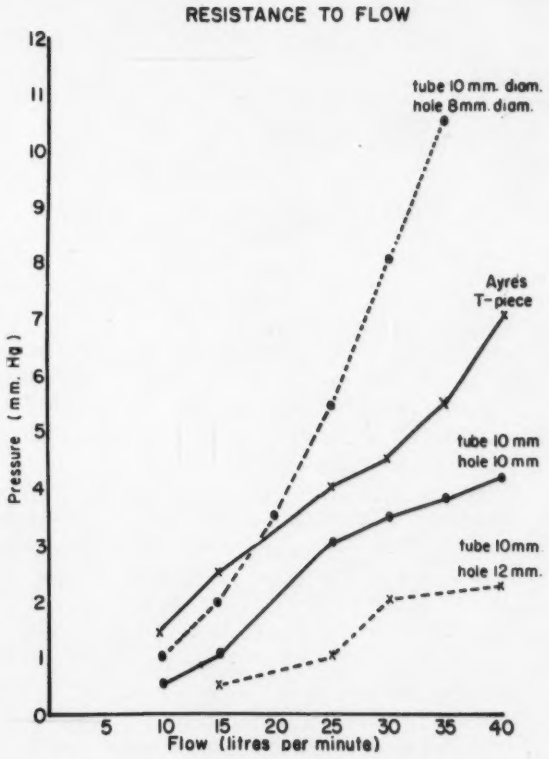

Figure 2

hole should be adequate considering the flow rates encountered with quiet breathing; a larger hole is impractical in view of the diameter of the tube.

To evaluate the effect of the flow-rate on the concentration of anaesthetic required for maintenance with our tube, we have plotted the changes in oxygen tension within our lung model every 30 seconds at flow-rates of 3, 5, 7, and 10 L. of nitrogen. On the same scale we have calculated the nitrogen concentration (percentage) within the lung, representing the anaesthetic concentration obtained (Fig. 3). It can be seen that a steady state is reached within a few minutes,

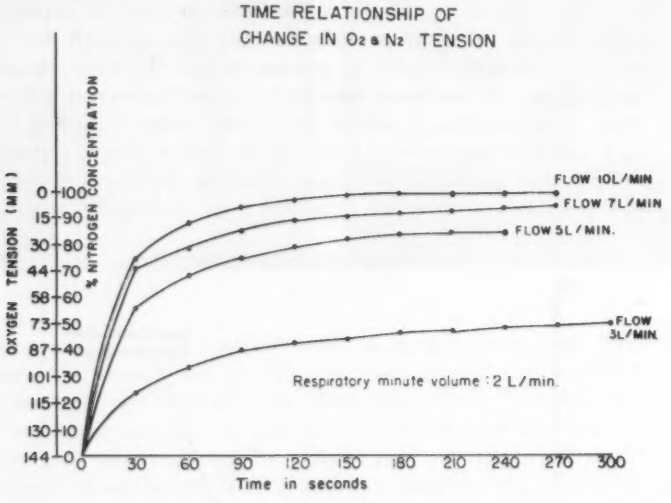

FIGURE 3

indicating that the steady state concentration of nitrogen in the lung depends on the rate of flow and, furthermore, that with a flow of nitrogen of 7 L. per min. there is less than 10 per cent admixture with room air and with higher flows 100 per cent concentration can be reached. Obviously an equilibrium is obtained earlier with the higher flows.

The second factor influencing the concentration of nitrogen is the ventilation of the lung. To be certain that the respiratory minute volume provided a basis for comparison, we determined the steady state concentration attained with a 5-L. flow of nitrogen, changing the respiratory minute volume once by changing the rate and another time by changing the tidal volume (Fig. 4). The results are not significantly different up to 5 L.; as expected, there is a tendency for the nitrogen concentration to be slightly lower with higher tidal volumes. Thus, it can be demonstrated that for a given respiratory minute volume, the nitrogen concentration in the lung increases in a linear fashion with the increase of nitrogen flow into the tube (Fig. 5) and that for a given flow of nitrogen into the tube the nitrogent concentration at a steady state will be inversely proportional to the respiratory volume (Fig. 6). In addition, the effect of changes

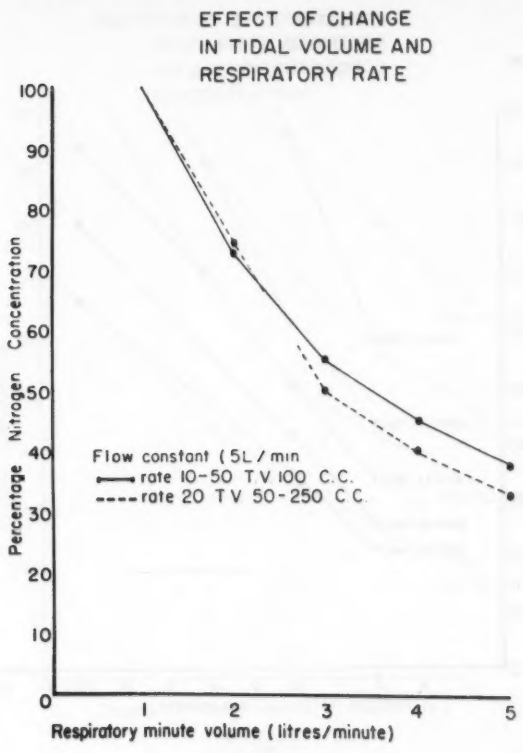

FIGURE 4

of the volume of the tube and the diameter of the expiratory hole were investigated; neither the length of the 1-cm. tube (the expiratory openings in constant relationship to the endotracheal tube) nor the diameter of the expiratory hole within a range from 6 to 12 mm. appeared to have a significant influence on the nitrogen concentration in the lung.

If we assume that a concentration of 75 per cent anaesthetic mixture is adequate for the maintenance of anaesthesia (with potent agents it is no problem to overcome a dilution by 25 per cent room air), we can construct from Figure 5 a graph relating the flow of anaesthetic gases to the respiratory minute volume. When plotting the respiratory minute volume and the nitrogen flow for 75 per cent nitrogen concentration in the lung model, we obtain an almost linear relationship within the tested range (Fig. 7). From the graph we can predict the required flow of nitrogen (or anaesthetic mixture), if we know the respiratory minute volume of the patient.

When comparing the efficiency of a T-piece with our system, we found no difference when the reservoir was not used (Fig. 8); by adding a reservoir of 10 ml., the nitrogen concentration was significantly increased. This greater

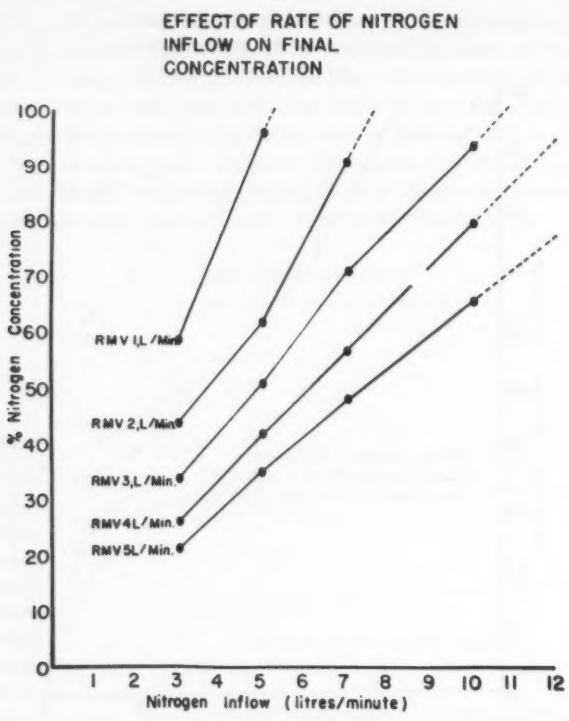

FIGURE 5

efficiency does not, however, improve the economics, since the higher gas flow needed in our system to maintain an adequate concentration of the anaesthetic mixture will be required to remove carbon dioxide from the reservoir in Ayre's technique. A comparison of recommended flow rates will demonstrate this (Table I). Based on data from Smith[10] the flow required according to Inkster's recommendation (2 × RMV) has been calculated. In the next column are the figures recommended by Ayre[2] as based on Hall's respiratory data[6] which differ considerably from those published by Smith.[10] Aside from this discrepancy, the flow recommended by Ayre[2] is practically identical with ours; it can be assumed, however, that with a reservoir the concentration of the anaesthetic will be close to 100 per cent, while with our flow rates only 75 per cent is obtained.

CLINICAL EXPERIENCE

The described modification of Ayre's technique has been used in 119 cases for the following surgical procedures.

Types of surgery	*No. of cases*
Face	25
Cleft lip/cleft palate	19
Neck	11
Ophthalmology	47
Others	17

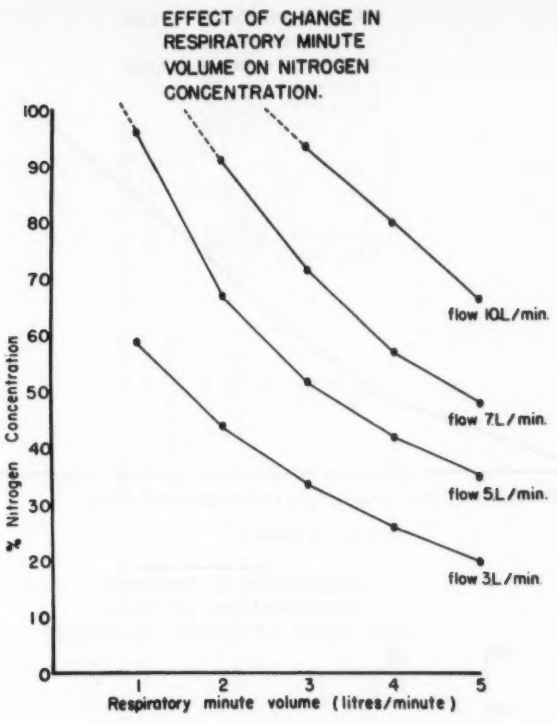

FIGURE 6

The age of these children ranged from one day to ten years; flows of 3–10 L. of a mixture of nitrous oxide and oxygen, supplemented by ether or fluothane, were used. In all cases satisfactory anaesthesia could be maintained and no difficulties or complications attributable to this technique were encountered.

CONCLUSION

It is felt that the presented modification of Ayre's technique, for which we do not claim any originality, has all the advantages of the original technique described, including the possibility to provide artificial respiration by intermittent occlusion of the expiratory opening. In addition the following points can be listed in its favour.

1. The equipment is exceedingly simple and can be improvised readily.
2. The anaesthetic concentration is predictable: this makes it possible to produce a stable anaesthesia and avoid over-dosage.
3. There is no re-breathing and no accumulation of carbon dioxide within the equipment.
4. This modification has even less bulk and weight than Ayre's T-tube and can be readily incorporated in drapes and other devices in situations where the surgeon likes to have the anaesthetic equipment out of his way.

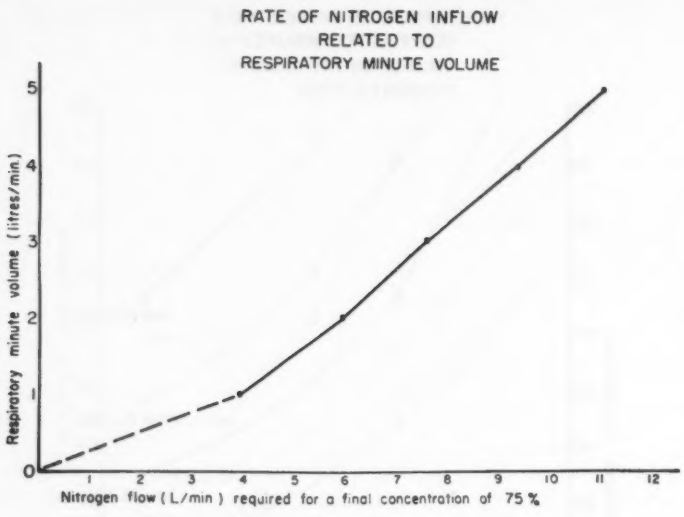

FIGURE 7

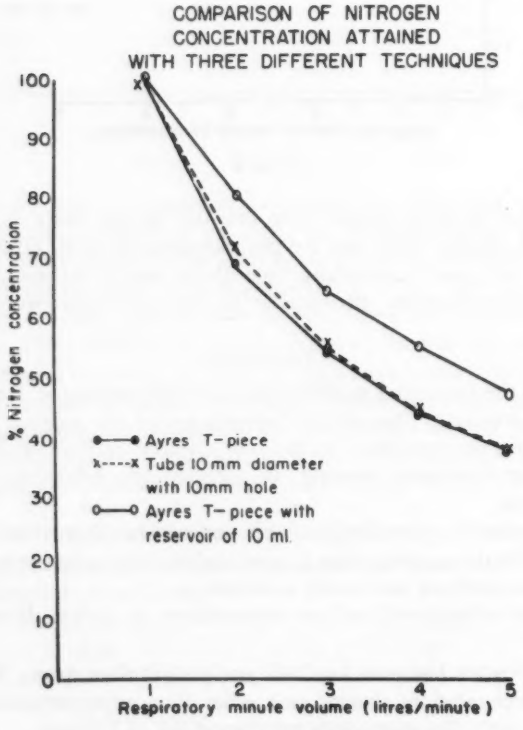

FIGURE 8

TABLE I

RESPIRATORY INDICES AT VARIOUS AGES AND FLOW REQUIREMENTS FOR AYRE'S TECHNIQUE AND FOR MODIFIED TECHNIQUE

Age*	Weight (lb.)	VT* (c.c.)	Frequency* (per min.)	RMV* (L./min.)	Ayre's technique			Flow required with modified technique§ L/min.
					Reservoir capacity‡ (c.c.)	Flow required‡ (2×RMV) L/min.	Flow recommended by Ayre† L/min.	
1 wk.	6.5	17	30	0.5	(0–5)	1.0	3.0	2.0
1 yr.	22	78	24	1.8	24	3.6	6.5	5.5
3 yr.	32	112	22	2.4	37	4.8	7.5	6.6
5 yr.	40	130	20	2.6	43	5.2	8.0	7.0
8 yr.	58	180	18	3.2	60	6.4	9.0	8.0

*From Smith.[10]
†Ayre.[2]
‡Calculation based on recommendation by Ayre[2] and Inkster.[7]
§From Figure 17.

Disadvantages may be that this anaesthetic system is slightly less efficient than Ayre's technique. The possibility of accidental distortion or occlusion of the expiratory opening was kept in mind, but was not observed in practice.

Summary

A modification of Ayre's technique, consisting of a piece of tygon tubing 1 cm. in diameter with an expiratory opening of the same diameter, was used in 119 cases with clinically satisfactory results. Carbon dioxide accumulation in the anaesthetic system is not possible, since there is no reservoir. The limiting factors are the expiratory resistance and the production of an adequate anaesthetic concentration in the lung. These two factors have been investigated using a model lung with variable changes in respiratory rate and volume; nitrogen represented the anaesthetic agent. The resistance was found to be acceptable. The concentration of nitrogen (anaesthetic gas mixture) in the lung was calculated from the measured changes in oxygen tension. Typical curves are presented for the effect of different rates of inflow of nitrogen and the influence of changes in respiratory minute volume on the nitrogen concentration in model lung. From these a graph was constructed from which the rate of flow of anaesthetic gas can be determined for a given respiratory minute volume in order to obtain an anaesthetic concentration of 75 per cent in the lung (or 25 per cent dilution of the anaesthetic mixture with air). The flow rates so determined were compared with data published by Ayre. It was concluded that this modification is only slightly less efficient than Ayre's technique, but has less bulk and weight than any other system in children. The technique is particularly useful in surgery of the head and neck in small children, where the tube will occupy a minimum of space and can be readily incorporated into the surgical drapes.

Résumé

Nous avons présenté une variation de la technique de Ayre, en employant un tube en Tygon de 1 cm. de diamètre avec un trou de 1 cm. de diamètre. Nous avons étudié expérimentalement la résistance expiratoire et les facteurs influençant la concentration de l'agent anesthésique dans le poumon.

Nous avons trouvé une relation étroite entre la vitesse de l'inspiration des anesthésiques et le volume minute respiratoire. Cela permit de prédire le débit de mélange anesthésique nécessaire pour un volume minute respiratoire donné.

Nous avons comparé la modification décrite et la technique décrite par Ayre et, à notre avis, la première présente des avantages dans son application clinique.

Nous avons donné un bref résumé de notre expérience avec cette technique.

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CONTINUOUS EPIDURAL ANAESTHESIA IN MULTIPLE FRACTURES OF THE RIBS*‡

MAURICE TRAHAN, M.D.†

IN OUR SURROUNDINGS, continuous epidural is used frequenlty to relieve vasospastic diseases of the extremities, which are the result of arterial, venous, or a combination of venous and arterial dysfunction; to improve the circulation of blood in arteriosclerotic lower extremities; as treatment for acute or sub-acute pancreatitis; and in many other conditions.

Since March 11, 1960, we have had the opportunity to introduce catheters for continuous epidural anaesthesia in cases of multiple broken ribs. The aim is to relieve the patient of pain and to increase his pulmonary ventilation. The most intensive pain is due primarily to atelectasis. The atelectasis that we usually see in these patients is pulling on the lungs, and is the main cause of pain, much more than the broken ribs.

We insert the catheter, between lumbar 1 and 2, cephalad. We prefer the lateral position, the use of a 3-inch, 16-gauge Tuohy spinal needle, and a no. 3 nylon ureteral X-ray opaque catheter, with bilateral openings. For analgesic drugs, 0.15 per cent Pontocaine® is used on most occasions for the following reasons: it gives an analgesia of the sensitive nerves for three hours or more, it contains no preservative that could be irritant, and it causes less catheter obstruction by its crystalization. On the first injection, 15 to 30 c.c. are necessary to relieve pain. Afterwards, 10, 15, or 20 c.c. every six or eight hours for four to eight days are sufficient. Following the epidural block, we inject Wyamine®, 5 to 15 mg. I.M. to prevent the possible fall of blood pressure due to sympathetic paralysis.

The following cases illustrate our results in patients treated in this manner.

Case 1

A man, aged 47 years, was wedged between two trucks. With thoracic and abdominal injuries he was admitted to the hospital on March 11, 1960. The patient was exhausted, anxious, agitated, afraid to move, and remained seated. His respiration, 24 per minute, was superficial. An X-ray showed fractures of the third, fourth, fifth, sixth, seventh, eighth, and ninth ribs on the right side, and of the ninth rib on the left side, with atelectasis of the right lung. Temperature was normal. Three hours after the patient's arrival, we introduced a catheter for continuous epidural, and injected 35 c.c. Pontocaine solution. Tactile analgesia was present from thoracic 2 to thoracic 10. The motor fibres were not involved. The analgesia appeared in less than five minutes and lasted for three to four hours. From then on, we injected 20 c.c. every eight hours for three days, and

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†Hôtel-Dieu de Quebec, Quebec, P.Q.
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15 c.c. the next four days. The patient could perform respiratory exercises, which promoted productive cough. Pulmonary atelectasis disappeared progressively. The epidural catheter was removed seven days later. Analgesics proved unnecessary during the remainder of the treatment.

Case 2

A 46-year-old house-keeper began to feel thoracic pains five hours after a sudden stop which projected her on the dashboard of her car. A dilaudid injection every four hours did not relieve her. Hospitalized on March 26, an X-ray revealed fractures of the fifth, sixth, seventh, eighth, and ninth ribs on the left side, with atelectasis of the left lung.

We inserted a catheter for a continuous epidural, and we injected 35 c.c. Pontocaine. The analgesia extended from thoracic 4 to the legs. Following the initial injection it was necessary to give 20 to 25 c.c. every eight hours to bring relief, and to give the patient the ability to maintain a clear respiratory tract. Three days later, we took out the catheter, because the patient, who had been treated in the past for alcoholic gastritis, developed delirium tremens. Forgetting the fractured ribs, the patient was treated only for this new incident.

Case 3

A man, age 37 years, was admitted to the hospital on August 11, 1960, eight days after a car accident. He was receiving pantopon every two hours, had difficult and noisy respiration at a rate of 24 per minute. He was referred for post-traumatic diaphragmatic hernia. To reduce costal pain, and above all, to allow productive cough, he was immediately put on a continuous epidural. For the next four days, the patient received alternatively, every four hours, 15 c.c. Pontocaine® or 100 mg. Demerol.® The patient was nauseous and vomiting. However, his respiration was improved.

Then the patient underwent a thoracotomy for a 4-inch breach in the diaphragm. The first postoperative day, he received alternatively, every four hours, 100 mg. Demerol and 17 c.c. Pontocaine. The second day, he received three injections of Pontocaine and two injections of Demerol, and had a good night's sleep. For the next four days, he received only three injections of Pontocaine each day. He performed his respiratory exercises and was ambulatory. Ten days postoperative, he was discharged in good health.

Case 4

A 39-year-old man was hospitalized following an accident on September 27. An X-ray revealed a fracture with displacement on the posterior axis of the third, fourth, fifth, sixth, and seventh left ribs, and pulmonary atelectasis on the same side. The patient expectorated blood. Inspiration was painful. Demerol did not bring relief for more than one hour. He refused aerosol therapy and respiratory exercises, because, he said: "this is too painful."

Two days later, we introduced a catheter for a continuous epidural block, and injected 20 c.c. Pontocaine, repeating 10 c.c. every six hours for the first two days, and every eight hours for the next five days. During this period, the patient was ambulatory, performed respiratory exercises, and was free from pain.

Case 5

A 60-year-old hotel-keeper fell on a desk. An X-ray taken on October 15, 1960, revealed a fracture with displacement of the seventh, eight, ninth left ribs, a pneumothorax on the same side, and an hemorrhagic suffusion of the right lung. He was in severe pain.

On the same day we inserted a catheter, and injected 10 c.c. Pontocaine every two hours. Each time, the injection permitted productive cough and painless respiration. On October 16 and 17, observing that the respiratory rate rose to 30 per minute, while pulse and temperature remained within the normal limit, we considered the possibility of incipient atelectasis. We loosened the chest strapping to allow deeper ventilation and, on the following day, the condition receded. We then gave Pontocaine every six hours for the next three days through the epidural catheter. The patient was discharged and blessed "the tube in his back."

Case 6

A 48-year-old lumber-jack was injured by a falling tree. An X-ray taken on October 20 revealed a fracture of the sixth, seventh, ninth, and tenth left ribs, and a crushed fracture of the eleventh thoracic vertebra. His respiration was superficial, at a rate of 26 per minute.

On October 21, we inserted a catheter for a continuous epidural block and for five days we injected 1 per cent Carbocaine every four to six hours. Pain relief was dramatic. His convalescence went on without analgesics.

Discussion

A continuous epidural block is superior to a paravertebral infiltration or a direct infiltration of the fractured area. These later procedures have to be repeated too frequently to give similar results. For the first injection, 30 c.c. 0.15 per cent Pontocaine is usually needed to provide relief. Afterwards, a volume of 10 to 20 c.c. of Pontocaine is sufficient to relieve pain. This represents a dosage much inferior to that used for repeated simple infiltrations.

To prevent the fall of blood pressure, we give a dose of a vasoconstrictor related to the quantity of Pontocaine injected.

After this experience, we believe, for the following reasons, that the continuous epidural anaesthesia deserves a part in the treatment of broken ribs: to relieve the pain; to promote productive cough and prevent atelectasis; to minimize the doses of narcotics.

Besides the usual contraindications for the epidural anaesthesia, there is danger of masking abdominal pathology.

Résumé

Depuis le 11 mars 1960, nous installons une peridurale continue dans les cas de fracture multiple de côtes.

Les buts de ce traitement sont: de soulager le patient; de permettre une tous productive, et ainsi de prévenir l'atélectasie; de minimiser les doses de narcotiques.

Nous croyons que la douleur est causée plus par l'atélectasie qui tire sur le poumon que par les côtes fracturées.

Comme substance analgesique, nous employons surtout la Pontocaine 0.15 per cent pour les raisons suivantes: parce qu'elle donne une analgésie des fibres sensitives pour trois heures ou plus; parce qu'elle ne contient pas de préservatif qui peut être irritant; parce qu'elle cause moins d'obstruction du catheter par sa cristalisation.

Pour la 1ère dose, 15, 35 c.c. sont nécessaire pour soulager le patient. Par la suite, 10, 20 c.c. aux six ou huit heures pour quatre à huit jours sont suffisants.

Nous injections toujours Wyamine 5, 15 mg. I.M. pour prévenir la chute possible de la tension artérielle due à la paralysie du sympathique.

Six cas sont rapportés avec ou sans déplacement des côtes fracturées. Un cas avec une hernie diaphragmatique accidentelle et un cas avec deux vertèbres dorsales écrasées. Tous ont été traités avec succès et nous croyons que nous devrions employer la péridurale continue dans les cas de fracture multiple de côtes.

ACKNOWLEDGMENT

This work has been prepared in the department of Anaesthesia at the Hôtel-Dieu de Quebec, Fernando Hudon, M.D., F.R.C.P.(C.), Director, and registered at: "le département des recherches médicales, Hôtel-Dieu de Québec."

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EMPLOI DU FLUOTHANE EN ANESTHÉSIE DENTAIRE

LUC PERREAULT, M.D.*

L'UTILISATION du Fluothane dans le cabinet du chirurgien-dentiste s'avère de plus en plus une amélioration sur les techniques employées antérieurement. Alors qu'avec les techniques précédentes, le chirurgien se limitait la plupart du temps à des procédures aussi brèves que possible et travaillait à la hâte pour abréger la durée de l'anesthésie, il peut maintenant envisager des procédures beaucoup plus longues sans craindre le réveil trop hâtif du patient ou l'hypoxie prolongée que causent de trop fortes concentrations de protoxide d'azote.

La présente étude porte sur une série de 300 cas d'anesthésie au bureau du dentiste: 20 pour cent furent des adultes et 80 pour cent des enfants. Pour les adultes, l'âge variait de 15 à 60 ans alors que l'anesthésie fut administrée à des enfants de 2 à 15 ans, la moyenne se situant entre 4 et 10 ans.

En général, seuls les sujets correspondant aux risques I et II de la classification Saklad-Meyer furent acceptés. La durée de l'intervention variait de cinq minutes à 1.30 heure avec une moyenne de 30 minutes. Le genre d'intervention s'est limité la plupart du temps aux extractions et aux obturations dans un rapport de 30 pour cent d'extractions pour 70 pour cent d'obturations. Les cas d'obturations se sont rencontrés à peu près tous chez les enfants. Il y eut trois cas de chirurgie chez l'adulte dont deux cas de dents incluses et un cas d'alvéolectomie.

La préparation des sujets est la plus simple possible. Le jeûne de quatre à cinq heures est exigé. On ne donne pas de prémédication, quoique il nous est arrivé au début de la série de donner aux enfants nerveux ½ grain de nembutal. Par la suite, nous avons préféré la préparation psychologique par le dentiste au cours de la ou des visites antérieures.

L'appareillage employé est aussi simple. Un appareil Heidbrink portatif (Fig. 1), un vaporisateur à Trilene fixé à la sortie des gaz, un inhalateur nasal no 6 (Ohio) (Fig. 2) constituent l'essentiel de l'instrumentation. Quelquefois, chez les jeunes enfants, nous avons employé la valve MIE avec un petit masque malléable (Fig. 3) qui s'adapte bien à la respiration nasale. L'intubation oro-trachéale fut employée dans un cas de chirurgie, mais ne s'est pas avérée supérieure à la technique du nasque nasal.

L'induction se fait avec le patient en position assise. Chez l'enfant, elle est conduite assez rapidement avec le mélange N_2O/O_2 en proportions égales auquel on ajoute rapidement des concentrations croissantes de Fluothane. La même technique est employée chez la plupart des adultes. Dans certains cas, par exemple les hommes costauds ou certaines femmes qui le désirent absolument, nous employons du penthotal pour amorcer l'induction, les doses données variant entre 150 mg. et 300 mg. Lorsque nous employons le penthotal, nous donnons

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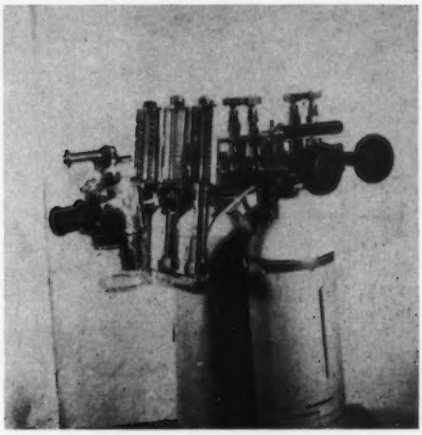

FIGURE 1

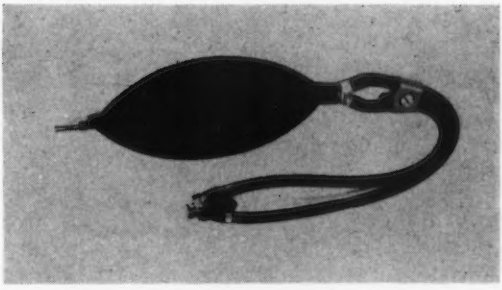

FIGURE 2

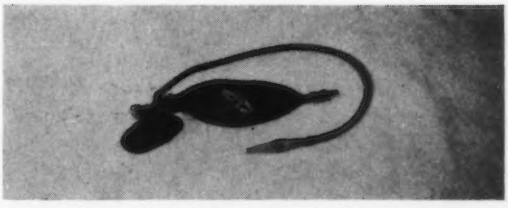

FIGURE 3

toujours la plus petite dose susceptible de provoquer le sommeil de façon à éviter une prédominance vagale qui favoriserait l'hypotension.

La maintenance se fait avec Protoxide-Fluothane-O_2. Le débit total variant entre 8 à 10 L. et quelquefois davantage, surtout au cours des procédures prolongées où l'on s'efforce de donner un débit/minute supérieur au volume/minute du patient de façon à prévenir au maximum la réinspiration qui favoriserait une

rétention de CO_2 et qui modifierait les concentrations de Fluothane dans l'atmosphère inspiré.

Lorsque le patient a atteint le degré d'anesthésie désiré, on place l'ouvre-bouche et un barrage pharyngé bien étanche. Ce barrage prévient la respiration orale et empêche les corps étrangers (sang, amalgame, etc.) de descendre dans le larynx et de là dans les bronches.

L'ouverture du vaporisateur varie avec le débit des gaz et la température du liquide, mais dans la moyenne des cas, une ouverture aux ¾ procure une anesthésie juste assez profonde pour abolir la réaction à la douleur. La position centrée des globes oculaires, le degré de dilatation pupillaire, la vitesse du pouls et l'absence de signes témoignant d'une réaction à la douleur sont les principaux critères sur lesquels on se base pour juger de la profondeur de l'anesthésie. En aucun temps, on tolère une mydriase fixe que l'on considère comme un signe d'une anesthésie trop profonde. L'amplitude respiratoire est bien surveillée de même que la perméabilité du nasopharynx. Dans les cas où l'on note une résistance à la respiration, une luxation antérieure du maxillaire inférieur fait disparaître cette résistance.

Les avantages de cette technique sont nombreux. Pour le patient, l'induction est agréable, tant pour l'adulte que pour l'enfant. Le réveil est rapide et après quelques minutes, l'élimination est à peu près complète, de sorte que le patient se sent très bien. L'absence de nausées et de vomissements est remarquable tant dans la période du réveil que dans les heures qui suivent l'anesthésie. Aussi 95 pour cent des sujets peuvent commencer à s'alimenter environ deux heures après la fin de l'anesthésie. L'absence d'hypoxie au cours de l'anesthésie contribue pour beaucoup à la sécurité de la technique et au bien-être du patient au réveil. La pression artérielle que l'on peut apprécier par la qualité du pouls ne subit jamais de chute importante, et la bradycardie n'est jamais marquée.

Du côté de l'opérateur, les avantages ne sont pas moindres. Les cauchemars et l'agitation de la période d'induction si souvent observée avec le protoxide d'azote sont absents avec le Fluothane. La puissance du Fluothane permet d'obtenir un plan d'anesthésie suffisant pour éliminer la réponse aux stimuli douloureux et par conséquent procure une tranquillité absolue pour l'opérateur. En même temps, le relâchement du maxillaire et du pharynx est complet et permet de placer avec facilité l'ouvre-bouche et le tampon pharyngé. L'absence de salive et la sécheresse complète des muqueuses est un autre avantage très important qui procure des conditions idéales pour les obturations. De tous les cas d'obturations pratiquées selon cette technique, seulement deux enfants ont développé des abcès sur une dent réparée, et dans les deux cas, il s'agissait de caries très profondes où le dentiste a tenté une obturation mais en évaluant d'avance les chances de succès comme minimes. Enfin, le Fluothane a comme dernier avantage d'être un des seuls anesthésiques à allier en même temps la puissance et la non-explosivité.

Comme désavantage, il faut noter le danger de surdosage. Le produit a le défaut de sa principale qualité: en effet, sa puissance est telle, que le dosage doit être constamment surveillé et les signes d'anesthésie notés avec attention. Le coût du produit est un autre facteur à considérer, mais les quantités nécessaires pour une anesthésie dentaire sont assez minimes de sorte que le prix de revient

quoique supérieur au protoxide seul ou associé au pentothal, demeure encore dans des limites convenables.

Au cours de ces 300 cas, aucun accident n'est survenu chez les patients anesthésiés avec du Fluothane. Seul un cas de lipothimie avec pâleur des téguments et transpiration fut noté: il s'agissait d'une jeune fille de 18 ans qui, à notre insu, n'était pas à jeun depuis le temps requis. Le vomissement corrigea cet état d'hypervagotonie.

Résumé et Conclusion

Il s'agit d'une observation portant sur 300 cas d'anesthésie au protoxyde-Fluothane-O_2 chez le dentiste. Quatre-vingt pour cent des cas étaient des enfants entre quatre et dix ans pour la plupart. La technique s'est avérée avantageuse au point de vue sécurité pour le patient, et facilité de travail pour l'opérateur. Elle offre l'avantage de pouvoir pratiquer des obturations dans des conditions idéales chez des enfants qui, autrement, auraient dû subir des extractions dentaires.

Le Fluothane employé en anesthésie dentaire s'est révélé une technique sûre et efficace, et apporte une amélioration sensible, surtout en ce qui regarde la conservation des dents chez les enfants.

Summary

This is an observation of 300 patients who underwent general anesthesia with Nitrous-Oxide-Fluothane-O_2 for dental treatments of some kind or other. Eighty per cent of those patients were children whose age ranged from 2 and 15 years, with an average age of 4–10 years.

The technique used has proven useful because it is safe and permits the dentist to work more freely. Fluothane has the advantage of producing dryness of the mouth and so gives ideal conditions for filling teeth which would otherwise be extracted.

LETTER TO THE EDITOR

Department of Anaesthetics,
The Royal Infirmary,
Manchester, England

SIR:

The remarks of Professors Wyant and Dobkin (CASJ *8* (1): 287 [May, 1961]) do not appear to be closely related to the facts of our case against the azeotrope. In our criticism we endeavoured to make two points which we believe are not unimportant in clinical anaesthesia:

1. The liquid azeotrope can be ignited in atmospheres of oxygen and nitrous oxide. If it is to be used with safety it is therefore essential to apply full antistatic and fire-protective measures when it is dispensed from conventional vaporizers with oxygen or nitrous oxide. I appreciate that mixtures containing a minute excess of the ether fraction are more dangerous in this respect. Perhaps my statement "azeotropic in all proportions" did not make this point so clearly as Boivin's; "No matter what the proportions in which Fluothane and ether are mixed, they will always tend to volatilize in azeotropic proportions" (CASJ *5* (4): 409 [Oct., 1958]).

2. Halothane and ether are pharmacologically incompatible in man, their cardiovascular effects being adversely additive. From a clinical point of view the method by which this effect was demonstrated may be regarded as "ludicrous"; but it is, nevertheless, a recognised pharmacological procedure. Incidentally, in a few cases investigated, the administration of ether after a period of halothane anaesthesia did not provoke signs of circulatory stasis: circulatory collapse appears to be dependent on the continued and simultaneous administration of both drugs.

In the numerous considerations of the relative merits of halothane and other agents, those concerning the azeotrope are by no means the most serious, the effects of the azeotrope being to a large extent controllable. The most disturbing reaction to the introduction of halothane has been the attempt to revive interest in chloroform. Despite Dobkin's arguments (Brit. J. Anaesth. *33*: 239 [1961]) chloroform remains virulently hepatotoxic, a fact which would seem to have been established beyond reasonable doubt by the tragic incidents courageously reported by Siebecker and Orth (Anesthesiology *17*: 792 [1956]); all the skill in the world will not eliminate this hazard.

MICHAEL JOHNSTONE, M.D.

BOOK REVIEWS

MODERN TRENDS IN CARDIOLOGY. Edited by A. MORGAN JONES. Toronto: Butterworth & Company (Canada) Ltd. 1960. $14.50.

AS THE TITLE would suggest, this book is not intended as a basic comprehensive text of cardiology. It is an anthology, by mainly United Kingdom authorities, of the more recent thinking and research in several selected fields relating to the cardiovascular system. Nearly half the book is given over to the metabolism, diagnosis, and handling of coronary artery disease, on a level which probably is not necessary to the anaesthetist, student or otherwise. In addition, there are chapters on somewhat esoteric subjects such as "Cardiac Muscle Metabolism," "The Kidney in Heart Disease," which touch on matters controversial enough to be as yet of no practical value. There are, however, a few chapters of interest to the anaesthetist: "Circulatory Dynamics and the Left Heart," "Pulmonary Function in Heart Disease," "Elevation of Pulmonary Vascular Resistance," "Atrial Septal Defect," and "Medical Aspects of Cardiac Surgery."

The book is expensively printed on coated paper, and has a comprehensive list of references at the end of each chapter. It cannot be unreservedly recommended as a text for anaesthetists.

T.R.H.

MODERN TRENDS IN ENDOCRINOLOGY (SECOND SERIES). Edited by H. GARDINER-HILL. Toronto: Butterworth & Co. (Canada) Ltd. 1960. $16.00.

THIS VOLUME, published some three years after the first series, fulfils its objective in enlarging upon its predecessor. It is therefore not a comprehensive survey of endocrinology, but a well-written and detailed account of the present day status of knowledge of specified aspects of endocrinology, and is intended for use with the first volume. The subject matter is very thoroughly covered from the clinical and laboratory points of view. The position in research in the endocrinology concerned is discussed at length and the pertinent laboratory diagnostic tests are described. In the section on treatment of tumors of the hypophysis the position of radiotherapeutics is discussed. The book would be most suitable for internists involved in this field, but to all physicians it would provide most enlightening reading.

J.H.K.

NEWS LETTER

The Annual Meeting

The Annual Meeting of the Society at the Seigniory Club was again a pleasant and profitable experience, in the tradition set in past years. One hundred and eighty-four anaesthetists were registered during the four-day meeting. The high calibre of the clinical and scientific programme held the attention of large audiences throughout the meeting, and the contribution by the exhibitors was of the high quality which has come to be associated with this meeting. Highlights of the Annual Dinner were the presentation of the first British Oxygen (Canada) Prize, divided between Dr. Lewis Hersey and Dr. Mary Morris (with Dr. Ronald Millar), and the installation of Dr. R. G. B. Gilbert as the new President of the Society. Highlight of the dance was the vision of a distinguished Professor and his Resident cooling their blistered feet (or were they bruises?) in the fountain.

A meeting of the heads of Departments of Anaesthesia in Canadian Universities was held at the Seigniory Club preceding the Annual Meeting of the Canadian Anaesthetists' Society. A profitable discussion was held on the teaching of anaesthesia. A second meeting has been planned to precede the meeting of the Society in 1962. Professor S. L. Vandewater of Queen's University has been appointed as Chairman.

The following programme has been announced for the meeting of the Ontario Division at Kingston, Ontario, on October 6 and 7, 1961, to be held at Etherington Hall, Stuart Street.

FRIDAY, OCTOBER 6

Theme: Complications during anaesthesia, including problems in this and the immediate postoperative phase of surgical management

Chairman: E. S. Russell

8:30–9:15 A.M.	Registration
9:15–9:45	Special Care of the Neonate. G. Robert Horne
9:45–10:00	Address of Welcome. G. H. Ettinger, M.B.E., B.A., M.D., D.M., D.SC., F.R.S.C., Dean of Medicine, Queen's University
10:00–10:30	Problems of Ventilation. David J. Power
10:30–11:00	Coffee Break; time to view exhibits
11:00–11:30	Pulmonary Complications. D. L. Wilson
11:30–12:00	Complications during Ophthalmological Surgery. D. A. Rosen
12:00–12:30	Hypotension. Jay J. Jacoby
12:30–2:00	Luncheon at Kingston General Hospital
Chairman: S. L. Vandewater	
2:00–2:30	Bleeding Problems. R. Kennedy Smiley
2:30–3:00	Cardiac Arrhythmias: Significance and Treatment. J. E. Fay
3:00–3:30	Break for tea; time to view exhibits
3:30–4:30	Panel on theme of the day. *Chairman*: S. L. Vandewater; *Members*: Jay Jacoby, David J. Power, J. A. Milliken
4:30	Annual Business Meeting
5:00–7:30	H.M.C.S. *Cataraqui*. Informal Reception

SATURDAY, OCTOBER 7

Theme: Emergency care of the injured patient

Chairman: D. W. S. BEST

8:30–9:30	Films. *Infant Resuscitation*, comments by DR. HORNE; *Closed Chest Cardiac Massage*, comments and discussion by DR. VANDEWATER
9:30–10:00	Haemorrhage and Assessment of Blood Volume. JAY J. JACOBY
10:00–10:30	Emergency Care of the Injured Child. A. W. CONN
10:30–11:00	Coffee Break; time to view exhibits
11:00–12:00	Panel on theme of the day. *Chairman*: E. S. RUSSELL; *Members*: R. B. LYNN, DAVID J. POWER, R. F. HETHERINGTON

NOTES

1. October 7 is Queen's Homecoming. Football Game—McGill *vs* Queen's—Oct. 7. The Medical Formal is scheduled for Friday, Oct. 6.
2. Accommodation will be scarce so make reservations early. Recommended accommodations include Capri Motel, Hotel La Salle, Princess Motor Hotel, Shamrock Hotel, La Salle Motel, Le Roe Motel.
3. Registration Fee of $5.00 includes luncheon on Friday.
4. Activities will be arranged on Friday for wives of physicians attending the meeting starting with a coffee party at 179 Earl Street.
5. Participants are asked to limit presentations to 20 minutes allowing 10 minutes for questions and discussion.
6. Facilities will be available to speakers for the projection of 3¼ × 3½ and 35 mm. slides.

PARTICIPANTS

D. W. S. Best, M.D.
Secretary-Treasurer
Ontario Division Canadian Anaesthetists' Society

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Chief Anaesthetist
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Lecturer in Medicine and Paediatrics
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S. L. Vandewater, M.D., F.R.C.P.(C.)
Professor of Anaesthesia
Queen's University

D. L. Wilson, M.A., M.D., C.M., F.R.C.P.(C.)
Associate Professor of Medicine
Queen's University

Saskatchewan Division

Dr. G. C. Ryan, having completed his residency in Anaesthesia at the University of Saskatchewan has now joined Associated Anaesthetists in Regina.

Ontario Division

Dr. Anne Fehrmann has been appointed to the Department of Anaesthesia of Grace Hospital, Toronto.

Dr. Cyril M. Kincaide, formerly of the Lahey Clinic, Boston, Mass., has been appointed to the Department of Anaesthesia of the Wellesley Hospital, Toronto.

MEETINGS

ONTARIO DIVISION
CANADIAN ANAESTHETISTS' SOCIETY
Kingston, Ontario
October 6–7, 1961

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS
FOURTH ANNUAL REGIONAL CONFERENCE
Wentworth-by-the-Sea, Portsmouth, New Hampshire
September 14–16, 1961

PREMIER CONGRÈS BELGE D'ANESTHÉSIOLOGIE
Namur, Belgium
Octobre 5–8, 1961
Dr. J. de Ville de Goyet,
Secrétaire
3, avenue de la Vecquée,
Namur, Belgium.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS ANNUAL MEETING
Statler Hilton Hotel, Los Angeles, California
October 23–27, 1961

CANADIAN ANAESTHETISTS' SOCIETY ANNUAL MEETING
Seigniory Club, P.Q.
May 14–15, 1962

FIRST EUROPEAN CONGRESS OF ANAESTHESIOLOGY
Vienna, Austria
September 3–9, 1962
R. Kücher,
General Secretary,
Medizinische Akademie IX,
Alserstr. 4,
Wien, Austria.

THIRD WORLD CONGRESS OF ANAESTHESIOLOGISTS
São Paulo, Brazil
September 20–26, 1964

BRITISH OXYGEN CANADA PRIZE

BRITISH OXYGEN CANADA LIMITED have made available the sum of $1,000 annually for the prize to be awarded by the Canadian Anaesthetists' Society for the best original work in Anaesthesia completed in Canada during the year preceding the award. The second such prize will be awarded at the time of the Annual Meeting of the Canadian Anaesthetists' Society in 1962. The following regulations apply:

Qualifications

(1) Applicant must be a resident in training in Anaesthesia or a practising anaesthetist.

(2) The study must be carried out in a Canadian Hospital or University, and must have been completed during the previous 12 months.

(3) The study submitted may be of a basic or clinical nature.

Submission and Selection

(1) Applicant's study is to be submitted in quadruplicate to the Secretary, Canadian Anaesthetists' Society, *prior to December 31st, 1961.* The paper should *not* contain the name of the author, which will be communicated to the Secretary in a covering letter only.

(2) Where more than one person has participated in the work reported, the application for the prize must be made in the name of one of them only.

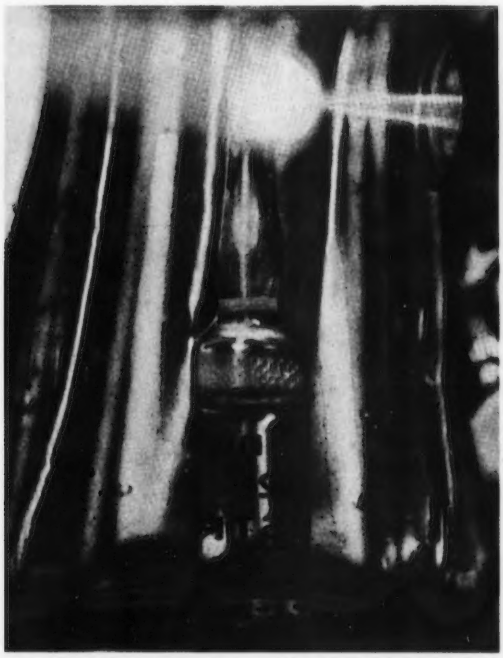
(3) Each applicant for the British Oxygen Canada Prize must be prepared to present such report in the programme of the Annual Meeting of the Canadian Anaesthetists' Society. The right of publication of all reports submitted in application for the prize is reserved to the Canadian Anaesthetists' Society Journal subject to acceptance by the Editor.

(4) Four (4) referees will be appointed by the Executive of the Canadian Anaesthetists' Society from departments of Anaesthesia in Canadian Universities. Not more than one referee shall be chosen from anv one University.

(5) In the event of two (2) applicants submitting work judged by the referees to be of equal merit, the award may be divided at the discretion of the referees.

(6) If in the opinion of the referees the studies submitted do not warrant the award being made in any year, the prize will be deferred.

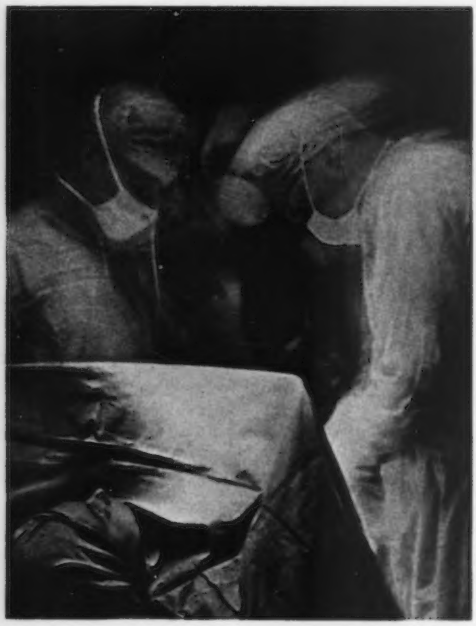
XYLOCAINE®
LOCAL ANESTHETIC



In the final analysis, only clinical experience can assure the survival of a drug. It is therefore gratifying to know that the performance of Xylocaine, in both dentistry and medicine, appraised in the light of current findings, confirms the original observations made more than a decade ago. Xylocaine has stood the test as a reliable and highly effective local anesthetic.

Surgery: infiltration nerve block and topical

Xylocaine is well suited for infiltration and nerve block techniques for a large number of major and minor operative procedures. Xylocaine gives anesthesia of adequate duration, is fast acting with high diffusibility, and its action is predictable. Minimal dosage consistently produces profound anesthesia. The margin of clinical safety is wide, and side effects, considering the extensive use of Xylocaine, are rare. For infiltration, 0.25% and 0.5% solutions are used in volumes of 30 cc. to 100 cc. The 1% solution may be used when smaller volumes of 10 cc. to 30 cc. are to be administered. When a single injection of Xylocaine is used for epidural, spinal and other



major nerve blocks, the concentration and volume varies with the type of block and the individual requirements. The total dosage of Xylocaine should *not* exceed 500 mg. when administered with epinephrine, or 300 mg. without epinephrine. Xylocaine is one of the very few local anesthetic agents which are effective topically as well as by injection. This is an important advantage in many surgical procedures where mucous membranes of the respiratory, upper gastrointestinal and lower genitourinary tracts, the eye and ear, and the anorectal area are involved. The 2% and 4% concentrations of Xylocaine solutions are used for topical anesthesia. Volumes are adjusted according to the requirements of the surgical procedures being undertaken.

Obstetrics, gynecology, urology: epidural & caudal, spinal "saddle block"

Spotty anesthesia, once a major drawback of epidural and caudal techniques, occurs only rarely with Xylocaine because of its high anesthetic index, wide diffusibility, short latency period, and adequate duration of nerve block. Its relative safety and reliability of performance has caused Xylocaine to be called a ". . . drug of choice for extradural analgesia."‡ Because of the specific dosage requirements for epidural anesthesia, strengths from 1% to 2% may be used. Many Canadian anesthetists prefer Xylocaine 1.5% for epidural anesthesia. This solution is now available without epine-

phrine or with epinephrine 1:200,000, packed in 30 cc. single dose containers. Operative anesthesia is obtained with volumes of 15 cc. to 25 cc. ■ "Xylocaine spinal" may be used with predictable results for obstetrical, gynecological and urological procedures, and for surgery of the lower abdomen and the lower extremities. "Xylocaine spinal" has a low binding affinity that minimizes potential nerve injury. Its anesthetic effect is routinely rapid, profound, well tolerated and free from "spottiness." It is completely stable in the presence of spinal fluid. The anesthetic action of "Xylocaine spinal" is of moderate duration, averaging 100 minutes, followed by another 40 minutes of analgesia.

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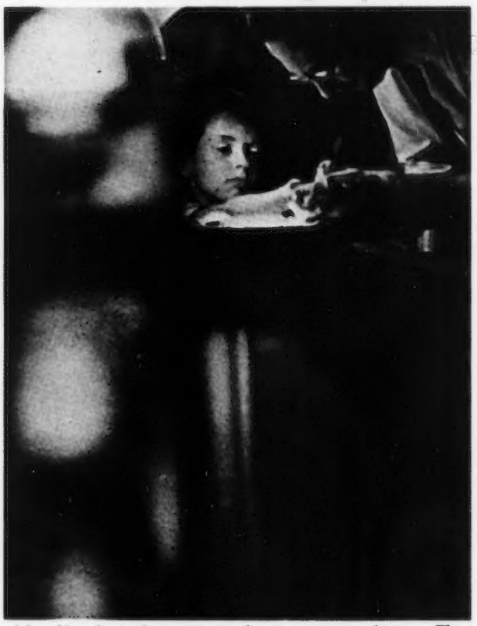
The general practitioner, the internist, and the surgeon alike are frequently called on to relieve pain or perform minor surgical procedures that may be successfully managed with the aid of this versatile anesthetic. Consistently effective anesthesia may be expected from Xylocaine because of its fast and profound action and spreading ability. It is virtually nonirritating to tissues and is relatively nonsensitizing, and possesses a wide margin of safety. For topical anesthesia Xylocaine may be applied as a spray, with cotton swabs, or by packs, as well as by instillation into a cavity and by application onto a surface. Local anesthesia of nerves, plexuses or terminal nerve endings requires individualized volumes and concentrations. For general use Xylocaine is recommended in concentrations of 0.5%, 1% and 2%, with the 2% solution generally used for nerve block. Minimal volumes of 4% Xylocaine may be used topically in those cases where lower concentrations are ineffective or inadequate. The 4% solution (in ampoules of 5 cc.) may also be used transtracheally and for retrobulbar injection.



Indications for topical application: Lacerations, abrasions, burns, corneal analgesia, indirect laryngoscopy, pruritus. Indications for injectable anesthesia: suturing, wound closure, causalgia, minor surgery, removal of moles, warts, and cysts, fracture reduction, bursitis, post-traumatic syndrome, herpes zoster.

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vials of 20 and 50cc., cartons of 1 and 5;
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Xylocaine HCl 4% without epinephrine
ampoules of 5cc., cartons of 10.

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Xylocaine HCl 5% with glucose 7.5%
(sp. gr. 1.030-1.035) 2cc. amps, cartons of 10.

FOR TOPICAL APPLICATION

Xylocaine HCl 0.5%, 1%, and 2% as described
above under Infiltration and Nerve Block.
Xylocaine HCl 4% without epinephrine (tinted
solution never to be used for injection)
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Also available for Topical Use:
Xylocaine Ointment 5%, tubes of 1 and ½ oz.
Xylocaine Jelly 2%, tubes of 30cc.
Xylocaine Viscous 2%, bottles of 100 and 450cc.

Write for manual "Xylocaine in Anesthesia"
and additional information for specific usage.

‡ Bryce-Smith, R.: Local analgesic drugs, Brit. M.J. 1:1039 (April 2)1960.

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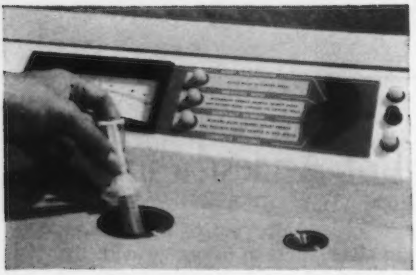

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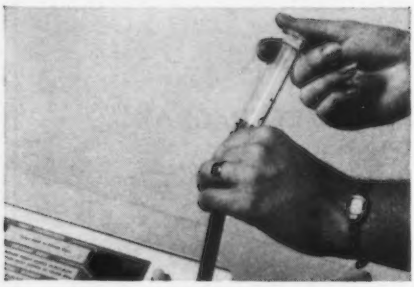

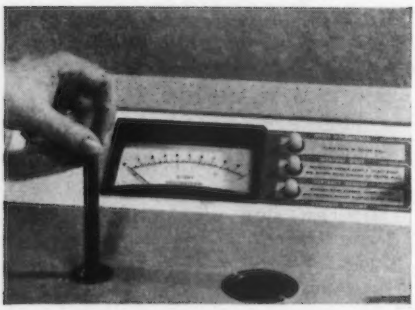

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THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

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